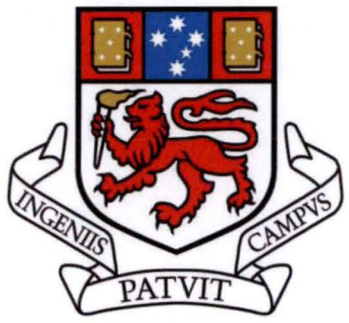
Regioselective Modification of Pyrroles – Applications towards Lamellarins & Pyrrolidine Analogues



UNIVERSITY OF TASMANIA

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BSc. (Hons)

Submitted in fulfilment of the requirements for the Degree of

Doctoral of Philosophy

School of Chemistry

University of Tasmania

May 2010

Dedication

This thesis is dedicated to the memory of my grandfather

Choi, Kam Chuen Anthony

Declaration of Originality

I declare that the thesis hereby submitted for the Doctor of Philosophy degree at the University of Tasmania is my own work and has not been previously submitted by me at another University for any degree. Where other sources of information have been used, they have been acknowledged.

Sarah Man Yee Ng

21st May 2010

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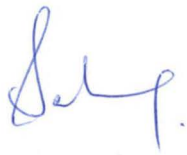

Sarah Man Yee Ng

21st May 2010

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Part III – Experimental

List of Publications

Copies of publications available on the CD provided.

(1) Smith, J. A.; Ng, S.; White, J. *Organic & Biomolecular Chemistry* **2006,** *4,* 2477-2482.

(2) Banwell, M. G.; Goodwin, T. E.; Ng, S.; Smith, J. A.; Wong, D. J. *European Journal of Organic Chemistry* **2006,** 3043-3060.

(3) Gardiner, M. G.; Jones, R. C.; Ng, S.; Smith, J. A. *Acta Crystallographica Section E-Structure Reports Online* **2007**, *63*, O197-O199.

(4) Gardiner, M. G.; Jones, R. C.; Ng, S.; Smith, J. A. *Acta Crystallographica Section E-Structure Reports Online* **2007**, *63*, O470-O471.

Abbreviations

^{o}C	Degrees Celcius
^{13}C NMR	Carbon Nuclear Magnetic Resonance Spectroscopy
^{1}H NMR	Proton Nuclear Magnetic Resonance Spectroscopy
AgOTFA	Silver(I) Trifluoroacetate
at	Apparent triplet
atm	Atmosphere
Bn	Benzyl
Boc	*tert*-Butylcarbonyl
Bu_4NF	Tetra-*n*-butylammonium fluoride
cat.	Catalytic
CBS	Corey-Bakshi-Shibata
COSY	Correlation spectroscopy
d	Doublet
DCC	*N,N'*-Dicyclohexylcarbodiimide
dd	Doublet of doublet
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-Dimethylaminopyridine
DMF	*N,N'*-Dimethylformamide
E	Electrophile
eqv.	Equivalent
Et_3N	Triethylamine

h	Hour
HIV	Human immunodeficiency virus
HRMS	High resolution electrospray isonisation mass spectroscopy
HSQC	Heteronuclear single quantum correlations
Hz	Hertz
IR	Infrared
J	Coupling constant (Hz)
KB	Ubiqitous Keratin-forming tumor cell line HeLa
m	Multiplet
MCPBA	3-Chloroperoxybenzoic acid
Me	Methyl
$(MeO)_2CO_2$	Dimethyl carbonate
MeOH	Methanol
mg	Milligram
MIC	Minimal bactericidal concentration
mL	Millilitre
mmol	Millimole
MS	Mass spectroscopy
N.R.	No reaction
$NaCNBH_3$	Sodium cyanoborohydride
NBS	*N*-Bromosuccinimide
NMO	*N*-Methyl morpholin-*N*-oxide

NOESY	Nuclear overhauser effect spectroscopy
$Pd(OAc)_2$	Palladium acetate
$Pd(PPh_3)_4$	Tetrakistriphenylphosphine palladium
PDC	Pyridinium dichromate
Ph	Phenyl
ppm	Parts per million
psi	Pounds per square inch
r.t.	Room temperature
R_f	Retention factor
S.M.	Starting material
TBAI	Tetrabutylammonium iodide
TBDMSOTf	*tert*-Butyl dimethylsilyl triflate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	*N*-Triisopropylsilyl
Ts	*p*-Toluenesulfonyl
$Zn(OAc)_2$	Zinc acetate

Acknowledgements

Firstly, I would like to thank my supervisor, Dr Jason Smith for his supervision and patience over the last few years. His extensive knowledge and understanding of chemistry, and enthusiasm for my work provide me with the support. Without his guidance and advice, I would not have got this far.

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Abstract

In the past few decades, an extensive family of structurally intriguing and biologically active pyrrolic natural products were recognised. Many of these compounds were isolated from marine organisms and show potent biological activity, and as such have been the focus of much synthetic effort. The synthetic approaches involve the synthesis of substituted pyrroles, as well as using the reactive parent pyrrole as a flexible building block for construction. Herein, by using pyrrole as the core of the construction, the syntheses developed will be reported in two parts: (1) Regioselective synthesis towards aryl pyrroles. (2) The reduction of pyrroles *via* catalytic hydrogenation, dissolving metals reduction, and by borohydrides.

Part I – Regioselective synthesis towards aryl pyrroles

Pyrrole is a unique aromatic molecule as it can readily undergo substitution at all five positions. However, obtaining the desired regioisomer can be difficult to control. If the regioselectivity of the substitution reactions at any given position could be controlled, then pyrrole would be useful as a template for the synthesis of substituted pyrroles. The controlled substitution of the pyrrole nucleus and the elaboration of these products into selectively substituted pyrrole containing natural products can now be reported. The key to regioselective introduction of substituents is the selective halogenation of the ring. Chloride acts as a blocking group at the most nucleophilic site while iodide can be introduced at less active

sites. Selective substitutions of the iodide through the Suzuki-Miyaura reaction, followed by removal of the chloride, allow the preparation of C3-, C4- and C5-aryl derivatives. We have applied this methodology to the synthesis of lamellarin Q dimethyl ether (**22**), an intermediate in the synthesis of lukinol A (**5**)[1] and other diaryl-substituted pyrroles.

Part II – Reduction of Pyrroles

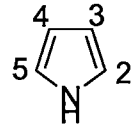
Methodologies for reduction of pyrroles have been reported previously, but have not been applied widely in synthesis. Pyrrole is a potential building block for the synthesis of pyrrolidine alkaloids and structural analogues. For example, if pyrrole can be reduced to a pyrroline *via* catalytic hydrogenation. This exploits regioselective pyrrole synthesis, followed by catalytic hydrogenation to form the saturated proline derivatives. Partial reduction of these relatively electron rich pyrroles is not possible *via* typical Birch reductions.[2] We now report a method for reduction of pyrroles to pyrrolines for the generation of a small compound library of pyrrolidine and proline analogues. Further *N*-sulfonyl derivatives can be chemoselectively reduced under mildly acidic conditions with hydride reagents to generate pyrroline building blocks. From these substrates, structural analogues of anisomycin (**99**)[3] with two and three carbons between the pyrrolidine and an aromatic ring can be generated in good yields over a few short steps. These methods can also be applied towards natural products of codonoposinine (**100**)[4] and preussin (**101**).[5]

Part I

Regioselective Synthesis of Pyrroles

Introduction

Pyrrole (**1**) is one of the most simple, electron-rich, five membered heterocyclic ring systems, initially found by Runge in coal tar in 1834.[6] After the structure was correctly identified by Baeyer in 1870,[7] many research groups developed and exploited the synthetic pathways used in creating pyrroles and their structural derivatives. For example, Paal and Knorr demonstrated a highly effective synthetic route, by the condensation of amines and 1,4-dicarbonyls.[8,9] This is still one of the major synthetic routes today.[10] Pyrrole compounds have also been found in many alkaloids and natural products, such as chlorophyll, heme,[11] and bile pigments.[6]

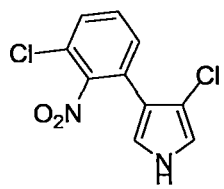


1

Aryl-Substituted Pyrroles

In recent decades, many substituted pyrrole-containing compounds have been isolated from natural sources and many have exhibited useful biological activity. For example, pyrrolnitrin (**2**) is an antifungal antibiotic, isolated from *Streptomyces pyrrocinia*.[12] Ensuring research showed that **2** and derivatives are active against *M. tuberculosis*[13] and possess anti-diabetic activity.[14] One of the top ten best selling drugs, the cholesterol-lowering compound, lipitor (**3**) is an example of a non-natural derivative that possess a 2,3-diaryl pyrrole unit as one of the key structural features.[15] Melvinolin (**4**), an aryl substituted pyrrole derivative, has also shown to

exhibit cholesterol-lowering activity, indicating the important role of aryl pyrroles in therapeutic compounds.[16,17]



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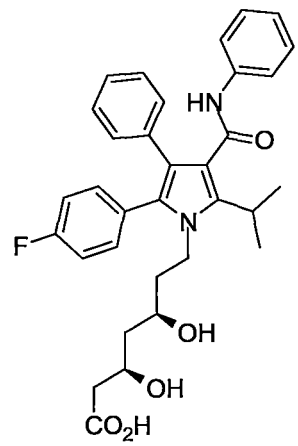

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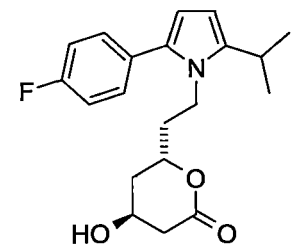
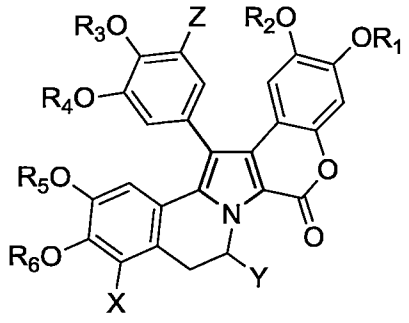


4

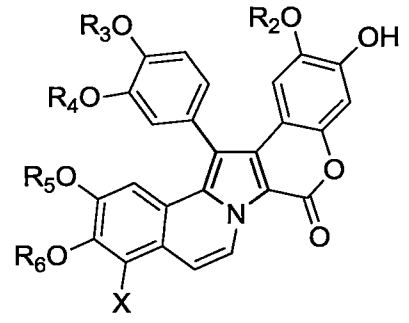
Lamellarins

A large group of poly-aryl substituted pyrrole marine natural products, referred to as the lamellarins, have been isolated.[18,19] This family has a common structural motif of a 3,4-diaryl or 3,4,5-triaryl pyrrole moiety and contains a carbonyl at C2.[20] (Figure 1) Lamellarins were first isolated and identified in 1985 from the Palauan marine prosobranch mollusc, *Lamellaria* sp.[21] Other lamellarin derivatives were then isolated from ascidians, tunicates, and sponges.[22-24] They can be found over a large region, including the southern Australian ocean,[23,25,26] the northeast coast of Australia[23] and the Indian Ocean.[26] Recently, more of these compounds were isolated from the Arabian Sea.[27] The lamellarin family includes over 30 naturally occurring pyrrole alkaloids to date.[24] These compounds have sparked interest due to their biological activity which includes cytotoxicity against several human tumour cell lines.[22] Lamellarin β showed cytotoxicity against human promyelocytic leukemia HL-60 with an IC_{50} of 4.8 μgmL^{-1}.[22] Not only are they a promising target

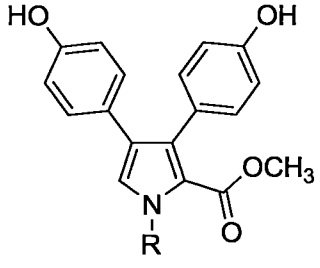
for new chemotherapy agents but they have also been reported to be active against HIV.[22,28,27]



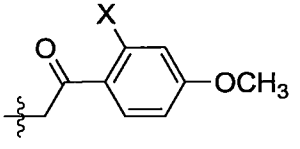
Lamellarin A, C, E, F, G, I, J, K, L , α, ε, β
R_1, R_2, R_3, R_4, R_5, R_6 = H, CH_3
X, Y, Z = H, CH_3, OCH_3, OH



Lamellarin B, D, H, M, N
R_1, R_2, R_3, R_4, R_5, R_6, X = CH_3, OH, H



Lamellarin P or O, R =

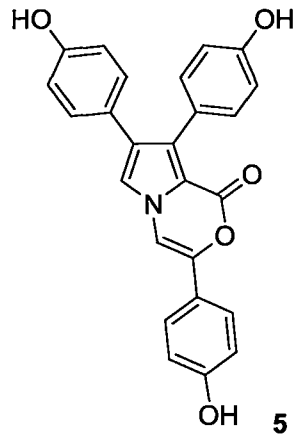


X = H, OH

Lamellarin Q, R = H

Figure 1 –Family of Lamellarins

Other similar poly-aryl substituted pyrroles include lukianol A (**5**) and ningalin B (**6**). Lukianol A was isolated from a tunicate collected from a lagoon off Palmyra atoll, and was shown to be active against human epidermatoid carcinoma with MIC of 1 μgmL^{-1} in KB cytotoxicity tests.[26,29,30] Ningalin B was isolated from an ascidian, collected from Ningaloo Reef in Western Australia.[31] While ningalin B is not cytotoxic, like number of the lamellarins, ningalin B and its derivatives have significant potential applications as they have been shown to play a role in reversing multi-drug resistance to human colon cancer cell lines.[32]



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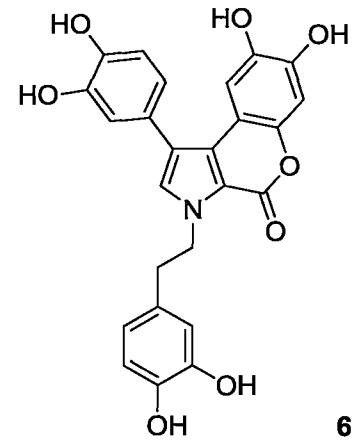


6

Combretastatin A-4

Many naturally occurring products play an important role in driving synthetic chemistry for confirmation of the compounds, or for the purpose of drug discovery by the synthesis of compound libraries. For example, lamellarins could be considered as a structural mimic of combretastatin A-4 (**7**), for which numerous structural analogues have been synthesised.[33] Combretastatin, found in the extracts of the African willow tree *Combretum caffrum*, is used in traditional medicines,[33] and is also a promising clinical candidate for the treatment of anaplastic thyroid cancer.[34,35] Because combretastatin has the ability to isomerise to the thermodynamically stable inactive *trans*-isomer; heterocyclic compounds that fuse the *cis*-orientation of the aromatic ring, such that lamellarins, are potential structural analogues.[33] (Figure 2)

Many of the reported syntheses for combretastatin analogues alter the bridge linkage to maintain the *cis*-confirmation of these structures.[35] On this basis, aryl

and diaryl pyrroles that contain the substructure of the lamellarins provide the subject of our interest.

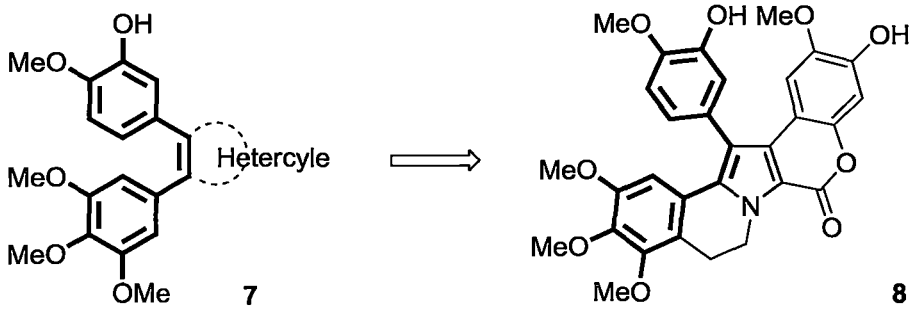
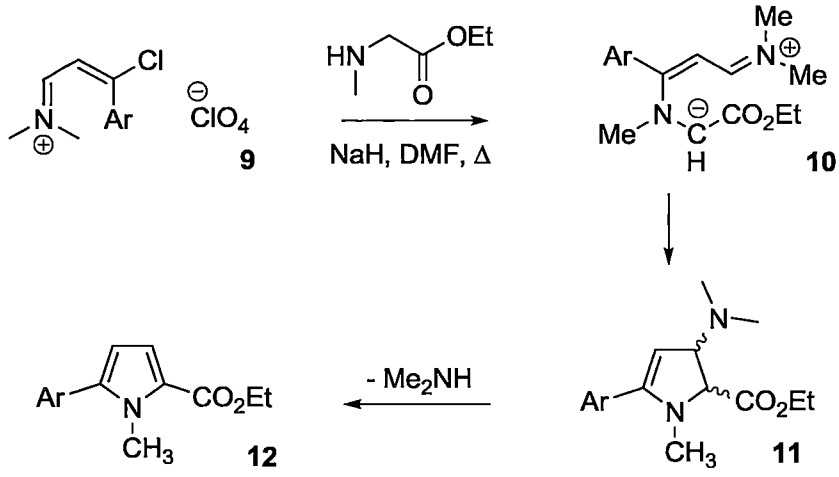


Figure 2 – Lamellarin C (**8**) as combretastatin A-4 mimics

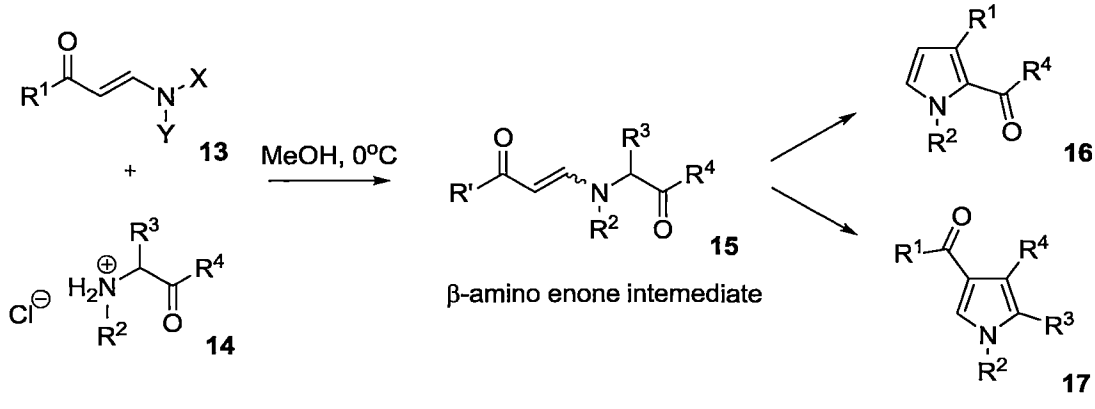
Synthetic Studies

Research groups have been exploring numerous general synthetic methods towards aryl-substituted pyrroles, but none are general for the synthesis of numerous targets. Most synthetic pathways involve the formation of the pyrrole ring by cyclisation, using an amine or amino acid derivative. For example, Gupton's group demonstrated that chloropropeniminum salt **9** reacted with an amino ester, giving an arylvinamidinium salt **10**, which ultimately forms a C5-aryl disubstituted pyrrole **12**.[36] (Scheme 1) This process employs conjugate addition, cyclisation and β-elimination. This simple formation of the chloropropenimium salt however is not trivial with yields of 44 % to 59 %.



Scheme 1 – Gupton's formation of substituted pyrroles

Alberola and co-workers also demonstrated that C3-aryl pyrroles can be synthesised with a β-amino enone **13** and α-amino ester **14**.[37] (Scheme 2) The β-amino enone intermediate **15** was formed by addition-elimination, followed by cyclisation either *via* an aldol condensation to give 2,3 disubstituted pyrrole **16**, or *via* the enamine onto the ketone to yield 2,3,4 substituted pyrroles **17.** While the starting materials and methods are more straightforward than the previous example, the use of this method is limited due to the resulting mixture of products formed.



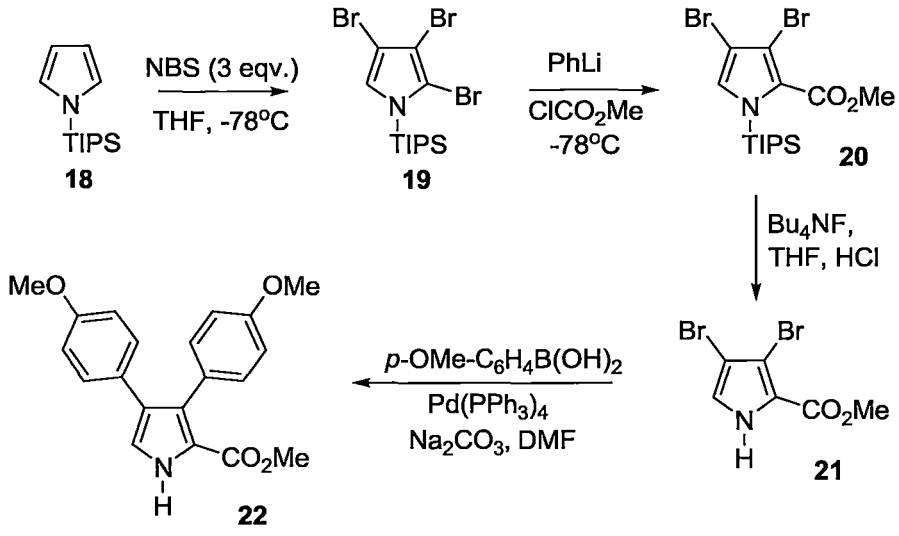
Scheme 2 – Alberola's synthetic scheme towards substituted pyrroles

Cyclisation is by far the most popular way of forming substituted pyrroles. However, they can be problematic due to the lack of reactivity and poor yields. More importantly, there is a lack of regioselective control. To date, there are no general syntheses which can form C2,3, C2,4 and C2,5-disubstituted pyrroles selectively.

Formation of Lamellarins

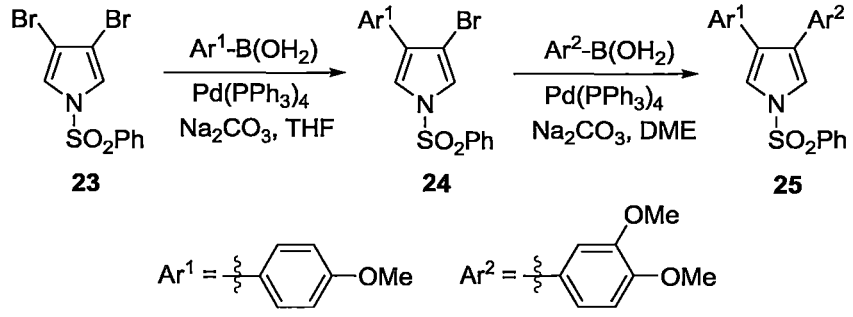
Many synthetic pathways used in the formation of lamellarins have been reported. They adopt two main strategies: (1) Starting from the pyrrole ring and functional groups, substituents can be introduced sequentially or (2) pyrrole rings can be formed with the substituents already in place.

For example, Banwell reported that lamellarin O and Q can be synthesised *via* palladium-catalysed cross-coupling reaction.[38] (Scheme 3) He reported that *N*-triisopropylsilyl (TIPS) can be used as the key for regiocontrol. The triisopropylsilyl derivative **18** was treated with three equivalents of *N*-bromosuccinimide (NBS) in THF at -78 °C, yielding the tribromo intermediate **19** with the most hindered positions being C2 and C5; hence the substitution pattern. Due to electronic effects, halogen-metal exchange occurs at C2, and reaction with methyl chloroformate yielded the ester **20** as a key cross-coupling precursor. This then underwent Suzuki-Miyaura cross-coupling with the appropriate aryl boronic acid, catalysed by $Pd(PPh_3)_4$ to give lamellarin Q dimethyl ether (**22**) in high yield.



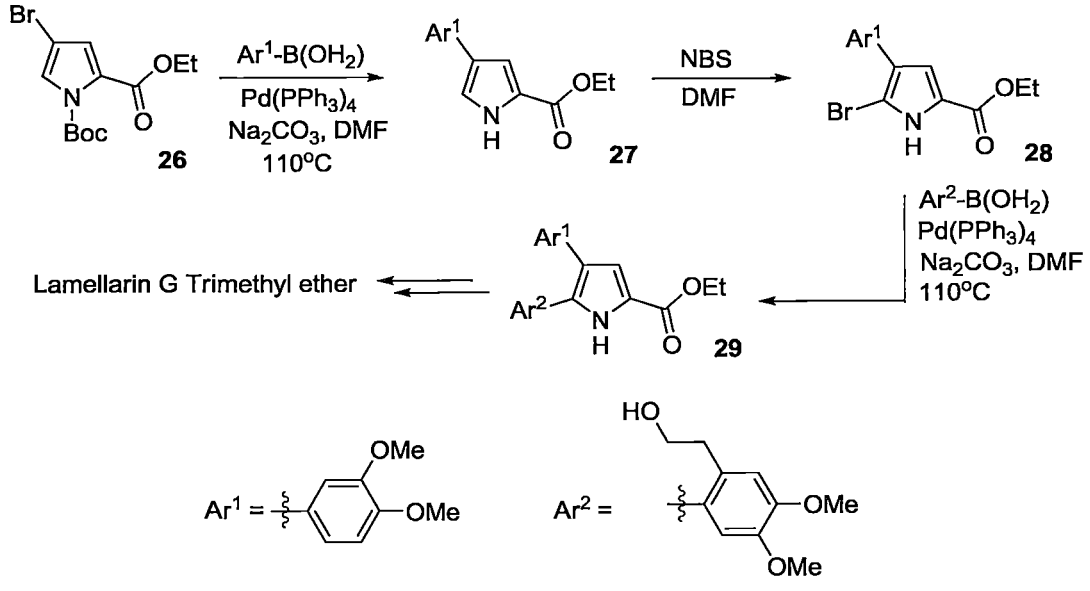
Scheme 3 – Banwell's palladium catalysed cross-coupling reaction

The formation of dibromo-*N*-phenylsulfonyl pyrrole **23** by the regioselective halogenation of *N*-phenyl sulfonyl pyrrole is another key coupling precursor for the synthesis of 3,4-diaryl pyrroles that was recently reported by Iwao.[39] (Scheme 4) A step-wise cross-coupling was the strategy for the formation of lamellarin derivatives. They demonstrated that mono-arylation was controlled by the sulfonyl group. Therefore, when one equivalent of boronic acid was used in the Suzuki-Miyaura cross-coupling reaction, mono-arylation was achieved in high yields. This was followed by another palladium-catalysed cross-coupling with a second boronic acid to give the 3,4-unsymmetricially arylated pyrrole **25**.



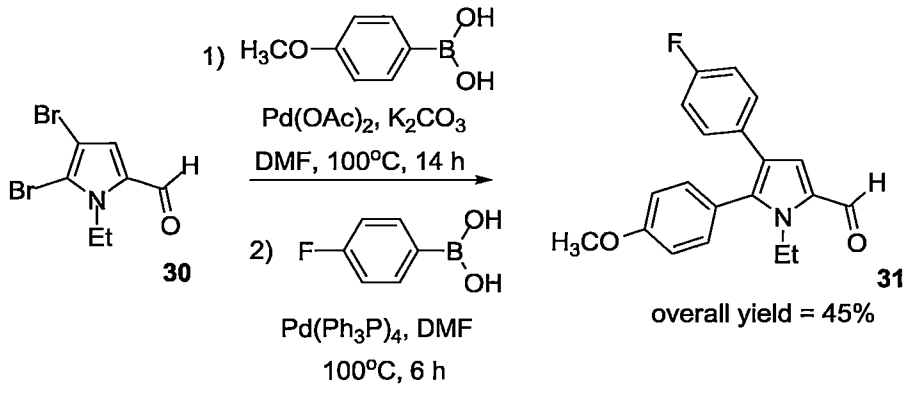
Scheme 4 – Synthesis of 3,4-diarylated pyrrole

Handy *et al.* also reported an example of a similar step-wise coupling process.[40] (Scheme 5) They showed a sequence of halogenation-coupling processes that result in regioselective control for the synthesis of 4,5 diaryl pyrroles. 4-Bromo-*N*-Boc-pyrrole **26** underwent the classical Suzuki-Miyaura coupling conditions, yielding the deprotected 4-arylpyrrole **27**. Regioselective bromination with NBS took place at the reactive C5 position, allowing the second coupling with another aryl boronic acid that contains an ethyl alcohol substituent. Intramolecular alkylation gave the 4,5-diarylated pyrrole **29** as a precursor to lamellarin G trimethyl ether.



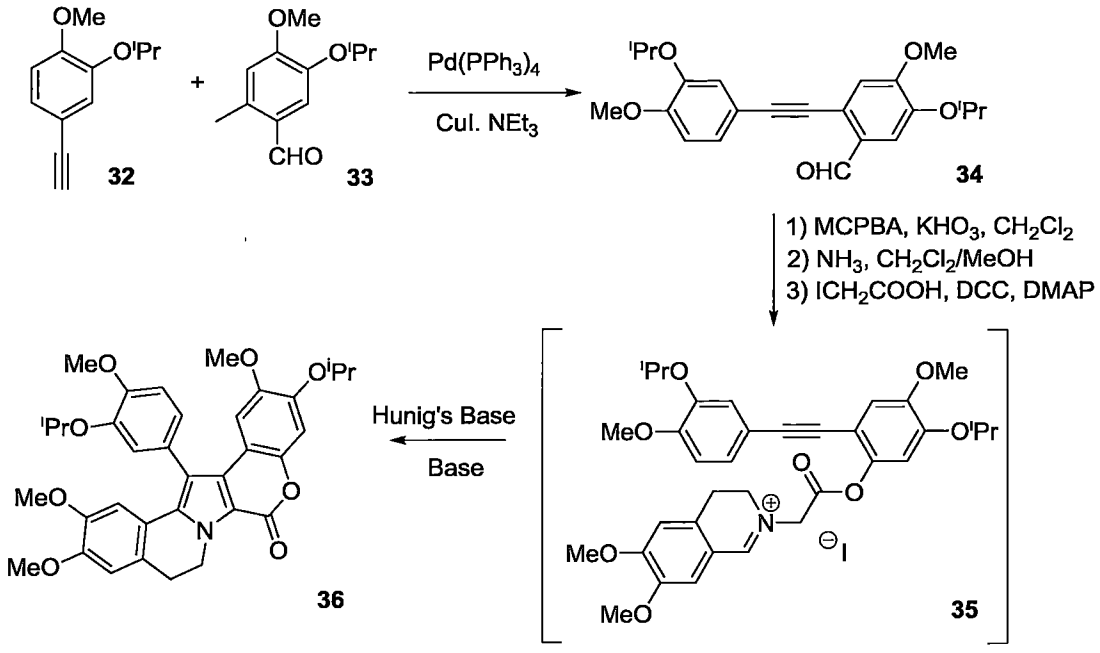
Scheme 5 –Synthesis of Lamellarin G trimethyl ether

Handy *et al.* are also the first to report a one-pot regioselective poly-coupling of pyrroles *via* Suzuki coupling.[41,42] (Scheme 6) The advantage of this reaction was the utilisation of the catalyst systems, such as palladium acetate and tetrakistriphenylphosphine palladium (0) to control the selectivity of the cross-coupling position and lead to the formation of the double-coupled product. Firstly, 4,5-dibromopyrrole aldehyde **30** underwent a standard Suzuki cross-coupling with palladium acetate as a catalyst under standard conditions, allowing regioselective aryl coupling exclusively at C4. This solution mixture immediately reacted with the second boronic acid and the addition of tetrakistriphenylphosphine palladium (0) catalyst to give a double coupled pyrrole **31** in 45% yield.



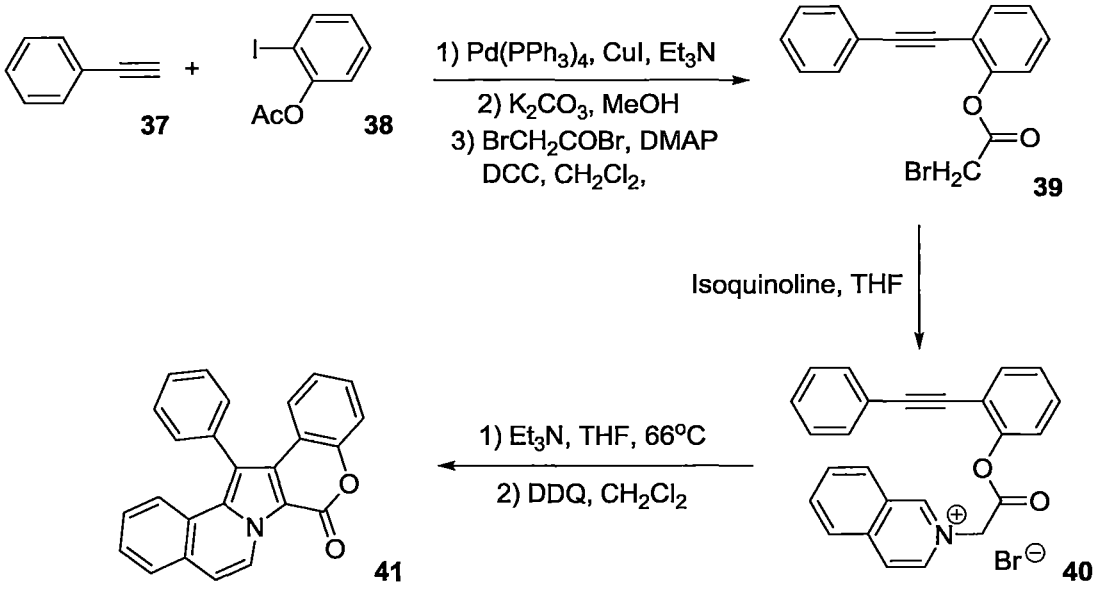
Scheme 6 – A one-pot regioselective Suzuki cross-coupling

In contrast to the sequential functionalisation of pyrroles, Faulkner reported a cycloaddition pathway for the formation of lamellarins.[27] (Scheme 7) This synthesis relied on palladium coupling and cycloaddition chemistry. Sonogashira coupling between phenylacetylene **32** and phenyl acetate **33** gave acetylene **34**, which was elaborated to form the intermediate salt **35** *via* oxidation, hydrolysis, and was then treated with iodoacetic acid. The intermediate salt underwent a [3+2] azomethine cycloaddition under basic conditions, and which undergoes auto-oxidation to yield a lamellarin derivative **36** in 54 % yield.



Scheme 7 – [3+2] Cycloaddition towards lamellarin derivatives

Another related example of an intramolecular cycloaddition was reported by Banwell, wherein the skeleton of the lamellarins were built.[43] (Scheme 8) Banwell also utilised a similar approach by carrying out a Sonogashira cross-coupling between **37** and **38**, followed by hydrolysis and treatment with α-bromo acetyl bromide to yield the ester before forming an isoquinolinium salt **40**. The azomethine ylide was formed after an immediate reaction of the salt with triethylamine. The ylide then underwent the [3+2] intramolecular cycloaddition forming a dihydropyrrole, which in this instance was oxidised with DDQ to give the parent ring system **41** for the lamellarins. This method was also applied to the synthesis of lamellarin N.[43]

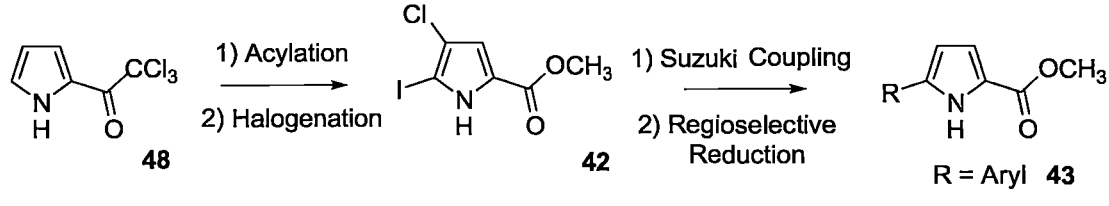


Scheme 8 – Intramolecular cycloaddition of azomethine ylide

Many lamellarins and pyrrole derivatives have been successfully synthesised. The syntheses for many of these often require acyclic starting materials specific for one target. Some of these methods are long, complicated and impractical for scale-up or application to compound libraries. More importantly, not many report regiocontrolled syntheses, and as such, there are no general methods to give all C2,3, C2,4 or C2,5-aryl-disubstituted pyrroles. Therefore, a new methodology towards the regioselective synthesis of substituted pyrroles using pyrrole as a template would provide a beneficial addition to literature.

Pyrrole is an electron rich heterocyclic ring, which is nucleophilic at all positions, due to the delocalisation of the lone pair on the nitrogen around to the ring system. The introduction of substituents can be selective in that C2 is most reactive position followed by C5, C3 and then C4, due to the electron density of these positions.

However, this can be controlled by the addition of a strong electron withdrawing group at C2, which reduces electron density of C5 and C3 (*pseudo-para* position), making C4 electron rich and more reactive.[44] This still limits this methodology to C2,4 disubstituted derivatives. In preliminary studies,[45] we demonstrated that this reactivity could be explored for the synthesis of C5-phenyl-2-carboxylate pyrroles by using a removable blocking group at the unwanted, but most reactive position; followed by substitution at the next most reactive site. This could be done by having a strong electron withdrawing group at C2. The trichloroacetyl group, for example, allows selective halogenation such as iodination or chlorination at C4. Chlorine was used as a blocking group and was introduced for masking the unwanted positions before iodination. Pyrrole halides then underwent palladium mediated cross-coupling to give the desired aryl-substituted pyrroles. (Scheme 9)

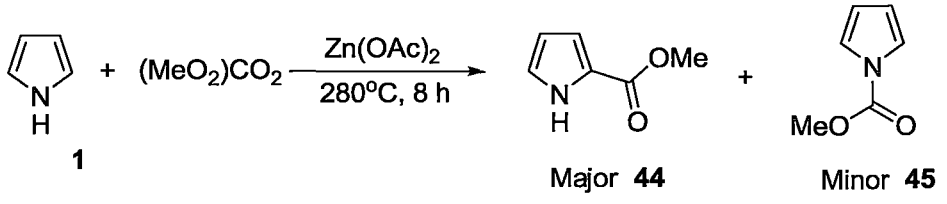


48 **42** **43**

Scheme 9 – Preliminary synthetic approach

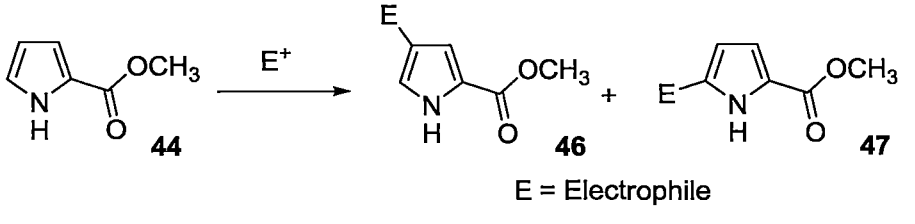
In many cases, such as lamellarin Q, an ester group or carboxylate group is at C2, therefore the introduction of an ester is required. Even though the most nucleophilic positions for a non-substituted pyrrole are C2 and C5, the introduction of an ester at C2 is not easily performed directly. A recent report by Fan showed a one-pot synthesis for the methyl pyrrole-2-carboxylate using dimethyl carbonate

($(MeO)_2CO_2$), with the presence of zinc acetate ($Zn(OAc)_2$) catalyst at a high temperature.[46] (Scheme 10) Other than the desired carboxylate **44** formed, a by-product of *N*-methyloxycarbonyl **45** was also observed. Although the conditions can be changed to optimise yields, the conditions are harsh (i.e. 280 °C) and not practical. Therefore, typically it is performed step-wise, i.e. formylation, oxidation and esterification.



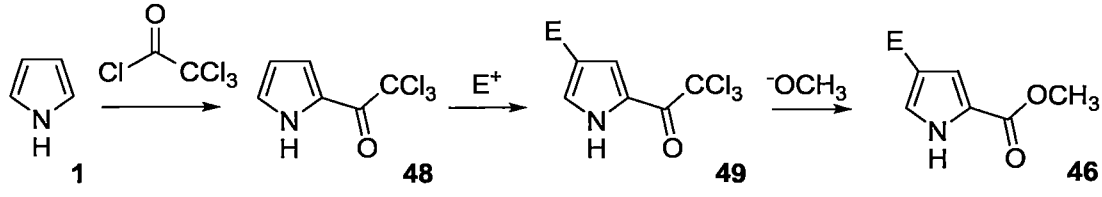
Scheme 10 – One-pot synthesis of methyl pyrrole carboxylate

Bélanger demonstrated that when halogenation, such as bromination, chlorination and iodination take place on a 2-carboxylate pyrrole **44**, a 1:1 mixture of C4 (**46**) and C5 (**47**) substituted pyrroles was obtained, which were inseparable by chromatography.[44] (Scheme 11) Hence, when an electron withdrawing group, such as an ester or formyl group is installed to a pyrrole, it reacts with electrophiles equally at C4 and C5. C3 and C5 were considered as *pseudo-ortho* and *para*, and are deactivated by the electron withdrawing group, but not significantly enough by an ester or aldehyde. Therefore, the ester cannot be present for selective halogenation and a stronger electron withdrawing group is required.



Scheme 11 – Non-selective Acylation

Bélanger *et al.* have exploited this *pseudo-ortho, para* deactivation by the presence of a strong electron withdrawing group such as the trichloroacetyl group.[44] By introducing this group at C2, simply by reaction with trichloroacetyl chloride, electrophilic substitution takes place exclusively at C4, hence *pseudo-meta.* This is because the strong electron withdrawing group has the ability to withdraw electron density from C5 and C3. Therefore C4 becomes the most electron rich position, and allows halogenation to take place selectively. The trichloromethyl ketone **49** can then be converted to a methyl ester **46** *via* the haloform reaction, which will be discussed in more detail later. (Scheme 12)



Scheme 12 – Electrophilic substitution of pyrroles

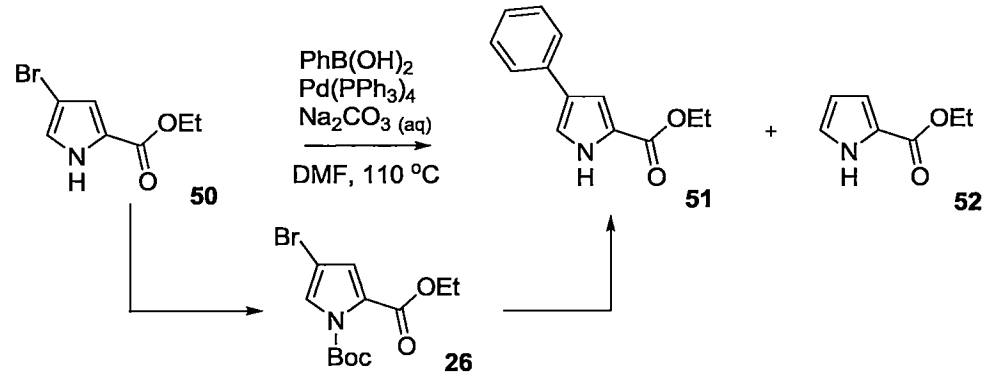
It was proposed that a removable blocking group could be introduced at C4, followed by substitution at C5. This could give a C2,5-disubstituted pyrrole after the removal of the blocking group. Therefore, if a brominated pyrrole underwent Suzuki-Miyaura cross-coupling, followed by the removal of the blocking group, the overall result of a selective C5-arylation could be achieved. The use of chlorine as a blocking group will also be discussed in more detail later.

Palladium catalysed cross-coupling is one of the standard methods for the formation of carbon-carbon bonds. These applications include Negishi,

Sonogashira, Stille, and Suzuki-Miyaura. The Suzuki-Miyaura reaction is by far the most commonly used. This was highlighted in a recent review by Banwell which summarised the various palladium catalysed cross-coupling reactions for pyrroles substrates, including the lamellarins.[6]

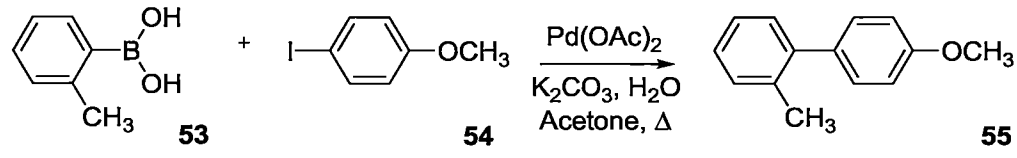
Pyrrole has been shown to be somewhat problematic for palladium-catalysed cross-coupling due to the high electron density of these systems, which can result in competing reductive dehalogenation.[47] Many research programs have developed and modified reaction conditions to improve the effectiveness of the cross-coupling. For example, Handy and co-workers exploited the chemistry of the Suzuki-Miyaura coupling of 4-bromopyrrole-2-carboxylates **50**.[47] (Scheme 13) They demonstrated that classical Suzuki-Miyaura coupling conditions using phenyl boronic acid with tetrakistriphenylphosphine palladium catalyst ($Pd(PPh_3)_4$) gave a 1:1 mixture of product **51** and dehalogenated starting material **52**. They proposed that due to the free *N*-H, a protecting group such as *tert*-butyl carbonyl (Boc) must be introduced in order to prevent dehalogenation and to obtain the arylated pyrrole **51** in high yield. During the reaction, it was noted that the protecting group was cleaved. It is possible that the conversion to the *N*-Boc derivative is not a protecting group manipulation, but has the effect of reducing electron density in the electronics of pyrroles. Therefore, it increases the rate of oxidative addition and the stability of the organopalladium intermediate which promotes the cross-coupling over the reduction elimination. It should be noted that this method was employed and extended to the formation of lamellarin G trimethyl ether as described previously.[40] Unfortunately, Handy's proposed Suzuki-Miyaura coupling

method is not ideal as it added an extra step in the activation of pyrroles. Therefore an efficient protocol for coupling halopyrroles was required.



Scheme 13 – Handy's modified Suzuki-Miyaura Coupling

During the previous work of the Smith group, the so-called ligandless catalysis for Suzuki-Miyaura coupling gave good yields of aryl pyrroles from the corresponding iodides.[6,45,48] (Scheme 14) This method was first reported by Beletskya in 1983. It simply involves the use of palladium acetate in either acetone or THF.[49] It was proposed that it eliminated two phosphine related side reactions, i.e. aryl-aryl exchange and phosphonium salt formation, in contrast with the classical Suzuki-Miyaura coupling reaction. The other effect was that phosphine catalysts slow the rate of oxidative addition to iodide.[49]



Scheme 14 – Ligandless palladium catalysed Suzuki-Miyaura coupling reaction

According to Novak, the main advantage of the ligandless Suzuki-Miyaura coupling is that it can improve reaction efficiency.[50] The modified condition allows shorter reaction times, under milder conditions with greater catalytic turnover. Under normal standard Suzuki-Miyaura coupling conditions, electron-rich and sterically hindered aryl groups are known to be difficult, because of their slow rate towards base-catalysed protodeboronation.[50] In the ligandless modified condition, electron donating and electron withdrawing substituents on either aryl halide or organoboronic acid, have been shown to have little effect. As a result, ligandless Suzuki-Miyaura coupling will be exploited to overcome the problem of pyrrolic systems.

Herein, manipulating the regioselective halogenation and the ligandless Suzuki-Miyaura coupling reaction, a new methodology is developed in the formation of mono-aryl pyrroles, and applies to poly-aryl pyrroles, such as those targeting lamellarins.

Chapter 1

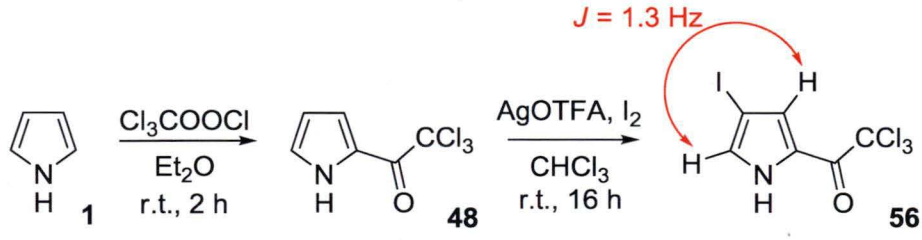
Formation of Aryl Pyrroles

Many aryl pyrrole-containing natural products have exhibited useful biological activities, with pyrrolnitrin (**2**) as in the example of 4-arylpyrroles. As mentioned in the introduction, there is a lack of general synthetic methodology for the regioselective synthesis of arylpyrroles, hence the formation of these analogues is targeted in this chapter.

1.1 Formation of C4-Aryl Pyrroles

The synthesis of an appropriately substituted pyrrole halide as an intermediate for the Suzuki-Miyaura cross-coupling is crucial in the formation of aryl pyrroles. This is because the position of the halide is the key; it directs the cross-coupling to take place. Bélanger, as well as previous experience within the group, have demonstrated that electrophiles can be selectively substituted at C4 on a trichloromethyl ketone intermediate **48**.[44,48] This ketone is the key intermediate in the formation of 4-aryl pyrroles. Thus pyrrole (**1**) reacted with one equivalent of trichloroacetyl chloride at room temperature for 2 hours to obtain the desired ketone **48** in 96% yield. (Scheme 15) The spectral data was compared and confirmed with the reported literature.[51] The ^{1}H NMR spectrum showed an apparent triplet at 6.39 ppm, a multiplet at 7.17 ppm, and a doublet of doublet of doublet at 7.39 ppm. This shows the substitution occurred at C2 which shifts the adjacent proton at C3 from ~6.38 ppm to 7.17 ppm. The presence of a strong absorption band at 1655cm^{-1} in the IR spectrum, as well as the resonance at 170 ppm in the ^{13}C NMR spectrum indicates the presence of the ketone.

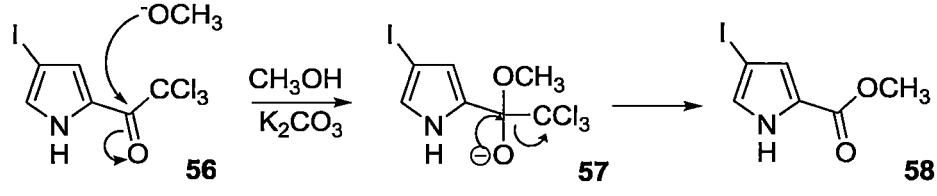
Iodine was used as an electrophile in this particular regioselective substitution, as iodides are better substrates for the proposed ligandless Suzuki-Miyaura cross-coupling.[48] Although iodine is a weak electrophile a silver salt was used to activate the iodide allowing rapid reaction with the pyrrole. Therefore iodine was added slowly into a mixture of **48** and silver(I) trifluoroacetate (AgOTFA) in chloroform and yielded the desired iodide ketone **56** in 86% yield. (Scheme 15) Silver trifluoroacetate was used as the Lewis acid to generate iodinium ions (I^+) or as a hypoiodoester,[52] which allows nucleophilic substitution to take place. Due to the loss of a pyrrolic proton, the ^{1}H NMR spectrum indicated two sets of doublet of doublets at 7.21 and 7.46 ppm representing the pyrrolic protons at C3 and C5; that coupled to each other with a coupling constant of 1.3 Hz supports the formation of the 4-iodo pyrrole **56**.



Scheme 15 – Regioselective iodination at C4

The trichloro ketone **56** can be converted to the methyl ester *via* a haloform reaction using alkaline methanol to form a carboxylate at C2. This key step is simply an acyl nucleophilic substitution, where methoxide is the nucleophile, and $-CCl_3$ is the leaving group, which is given off as chloroform to yield a methyl ester as the Suzuki-Miyaura-cross coupling precursor.[44,45] (Scheme 16) This reaction took place in accordance with the modification of the literature; it generated methoxide with

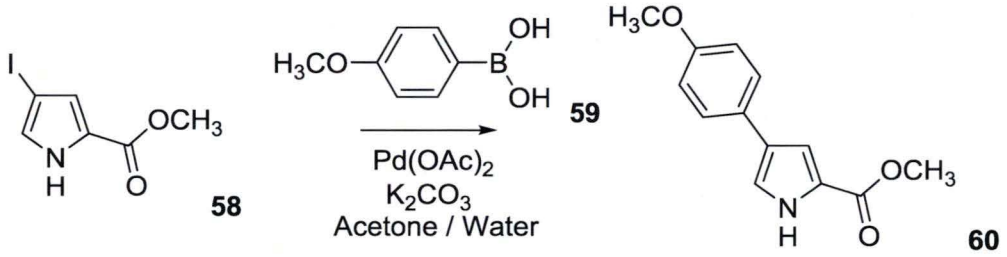
sodium metal,[53] by simply reacting pyrrole ketone **56** with methanol in the presence of potassium carbonate as the base at room temperature. The formation of the methyl ester **58** was shown by the appearance of a singlet at 3.86 ppm in the ^{1}H NMR spectrum, and a distinct methyl peak at 50.9 ppm in the ^{13}C NMR spectrum. Due to the presence of the less electron-withdrawing methyl ester, both the pyrrolic protons were shielded; hence the protons at C3 and C5 were shifted upfield to 6.97 and 7.01 ppm. IR spectroscopy also showed that the strong C=O absorption band shifted from 1655 cm^{-1} to 1689 cm^{-1}, i.e. a ketone to an ester. It was also noted that only one methyl ester peak was present, hence the reassurance that only one product, the 4-iodopyrrole methyl ester (**58**) and not a mixture of halogens, was formed.



Scheme 16 – Haloform reaction

Due to the advantages of the ligandless Suzuki-Miyaura-cross coupling, as demonstrated previously, the reaction conditions were exploited in our electron rich pyrrole system. The C4-iodo-pyrrole **58** was heated in a mixture of 2.5 equivalents of *p*-methoxyphenylboronic pinacol ester (**59**) in the presence of palladium acetate catalyst ($Pd(OAc)_2$), in acetone and aqueous potassium carbonate for 8 h. (Scheme 17) After column chromatography on silica gel and recrystallisation, the desired 4-aryl pyrrole **60** was isolated in 52% yield. The ^{1}H

NMR spectrum showed the addition of the *p*-methoxyphenyl substituent with the new resonances at 6.90 and 7.43 ppm for the aromatic protons, and a new singlet at 3.82 ppm for the methoxy group. The ^{13}C NMR spectrum also indicated the presence of the *p*-methoxyphenyl group by the resonance at 55.3 ppm, and the resonances in the aromatic region. Mass spectrometry gave a molecular ion of 231 $gmol^{-1}$ and was consistent with the formation of the 4-aryl pyrrole **60**. This compound was highly crystalline and the crystal structure was obtained, which confirms the regioselective functionalisation of the pyrrole core. (Figure 3)



Scheme 17 – Ligandless Suzuki-Miyaura Cross-coupling

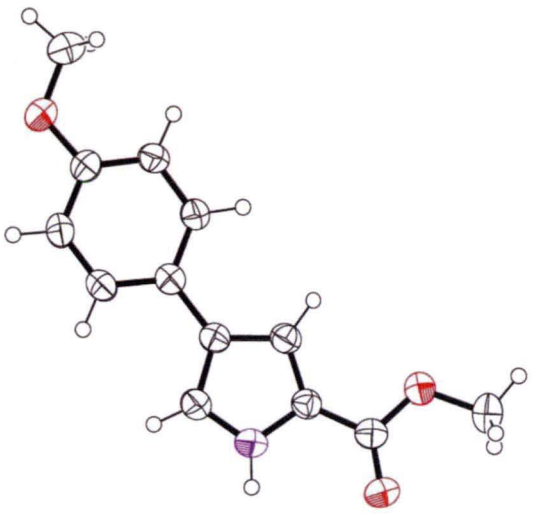


Figure 3 – An ORTEP diagram of compound **60** derived from X-ray crystallographic data (Purple = Nitrogen, Red = Oxygen)

During the isolation process, a by-product was identified. This by-product was caused by the protodeboronation from the base-catalysed system, and is one of the most common side-reactions under Suzuki cross-coupling conditions.[50,54-56,] This by-product was observed in the ^{1}H NMR spectrum of the crude reaction mixture, but the relatively non-polar material was readily removed from the product by column chromatography. More importantly, the dehalogenated product was not observed in the modified ligandless Suzuki-Miyaura cross-coupling reaction. Therefore, the *N*H group does not require protection or activation prior to cross-coupling.

The ligandless Suzuki-Miyaura coupling conditions were modified to optimise the yield. Firstly, and crucially, the reaction needs to be oxygen free because oxygen tends to destroy the palladium catalyst during the reaction process, turning the reaction mixture black (i.e. forming palladium black). The amount of boronic acid added to the mixture is also important because biphenyl is formed as a by-product from the boronic acids; hence excess is required. As a result, one equivalent of boronic acid and a second portion of the catalyst were added after the first hour of the reaction.

These modified ligandless Suzuki-Miyaura cross-coupling conditions were tested, giving the synthesis of a small series of 4-arylpyrroles; the isolated yields obtained were from 55% to 83% as shown in table 1. The result also indicated that boronate esters work equally as well as boronic acids in this system. Each compound was identified by spectroscopic analysis. All derivatives had not previously been

reported except for the chloro derivative **63** for which no data was reported.[57] In general, examination of the ^{1}H NMR spectrum indicated the pyrrolic protons, the methyl ester and the presence of signals for the aromatic protons that were introduced *via* Suzuki-Miyaura cross-coupling. Mass spectroscopy analyses also supported the characterisation with the correct molecular ions observed for the compounds. The spectral data for 4-phenyl derivative **61** was also in agreement with Arakawa.[58] In the case of the 4-*p*-tolyl pyrrole **62**, the crystal structure was obtained and reported.[59]

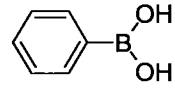
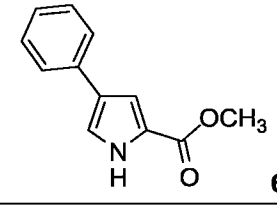
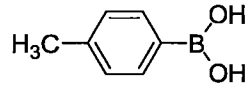
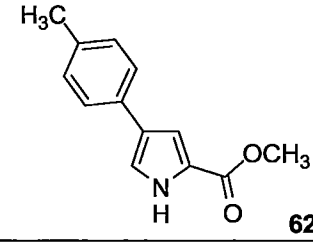
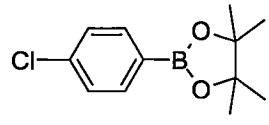
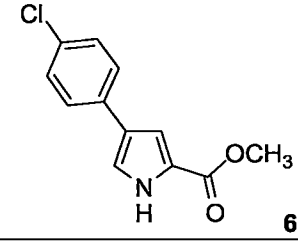
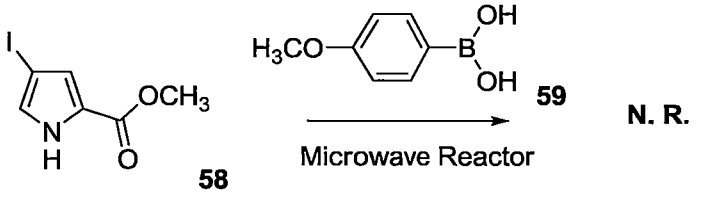
Aryl-Boronic Acid	Product	%Yield
	 **61**	83%
	 **62**	64%
	 **63**	55%

Table 1 – Results of the modified ligandless Suzuki-Miyaura Reaction

Recently much literature has reported the advantage of microwave-assisted Suzuki cross-coupling.[60-62] Microwave accelerated cross-coupling reactions were reported

to be convenient, have short reaction times, and be highly effective.[56,63] The ligandless conditions were compared with the classical Suzuki-Miyaura coupling conditions utilising a microwave reactor. Hence, to a 10 mL sealed pressure tube, a mixture of 4-iodopyrrole **58**, tetrakistriphenylphosphine catalyst, and *p*-methoxyphenyl boronic acid (**59**) in toluene or DMF were exposed to microwave heating in a CEM-Discover microwave reactor. (Table 2) The use of sealed tubes allows solvents to reach temperature above boiling points, whereas the change of solvents is required to increase temperature under conventional heating conditions. However, under the few conditions that were trialled, either recovery or decomposition of starting materials was observed. There were no noticeable products obtained in the short reaction times, even at 180°C. Hence the ligandless Suzuki-Miyaura coupling condition is superior for this pyrrole system.



			Microwave Conditions		
Catalyst	**Base**	**Solvent**	**Temp**	**Duration**	**Yield**
$Pd(PPh_3)_4$	$Na_2CO_{3\,(aq)}$	DMF	110°C	60 min	S.M.
$Pd(PPh_3)_4$	$K_2CO_{3\,(aq)}$	Toluene	120°C	60 min	S.M./D.
$Pd(PPh_3)_4$	$Na_2CO_{3\,(aq)}$	MeOH/Toluene	120°C	60 min	S.M.
$Pd(PPh_3)_4$	$Na_2CO_{3\,(aq)}$	MeOH/Toluene	180°C	60 min	D.

*S.M. = Starting Material, D. = Decomposition

Table 2 – Classical Suzuki-Miyaura Reaction *via* microwave reactor

1.2 Formation of C5 and C3-Aryl Pyrroles

This pathway for C2,4-aryl disubstituted pyrrole is a simple, elegant and straightforward method. By following the same method, C5 and C3-aryl disubstituted pyrroles can also be synthesised if halogenation can be effected with regioselective control. However, obtaining C3- and C5-iodo pyrroles is difficult due to the reactivity of these positions. During preliminary investigations, it was demonstrated that a removable blocking group can be introduced into the ring to mask the most reactive positions.[45,48,64] Chloride was found to be such an example of a blocking group. In comparison with iodide, it is effectively non-reactive under the proposed ligandless Suzuki-Miyaura cross-coupling conditions,[32,65] hence, coupling is expected to take place exclusively at the iodide. The chloride could then be removed easily at a later stage by catalytic hydrogenation.[45,48,64]

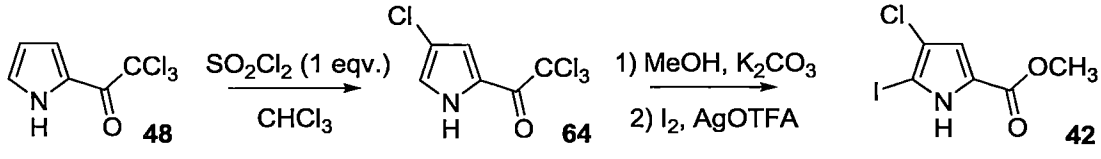
1.2.1 Formation of C5-Aryl Pyrroles

In the formation of C2,5-aryl disubstituted pyrroles, a blocking group at the more reactive C4 position is required, while an iodide is required at C5 for cross-coupling reaction. As demonstrated earlier, trichloromethyl ketone **48** allows regioselective substitution at C4. Therefore, manipulating **48** as the key intermediate, allows selective chlorination to be used to introduce chloride as the blocking group prior to the iodination at C5.

As a result, one equivalent of sulfuryl chloride (SO_2Cl_2) reacted with ketone **48**, as was reported by Belanger,[44] to give the 4-chloro pyrrole **64** in 83% yield. (Scheme

18) Examination of the ^{1}H NMR spectrum showed the loss of a pyrrolic proton at C4, which provoked a change in the splitting pattern to two sets of doublet of doublets. The coupling constant between the two pyrrolic protons was 1.5 Hz indicating the coupling between the protons at C3 and C5, and only the C4-substutitued pyrrole ketone **64** was obtained.

This was followed by the haloform reaction to convert the trichloromethyl ketone **64** to the known methyl ester derivative **65**. The ketone **64** was reacted with methanol and potassium carbonate at room temperature for 15 h to yield the methyl ester in 88%. The characterisation of this product was shown by the presence of a singlet at 3.86 ppm and 51.6 ppm in the ^{1}H and ^{13}C NMR spectra, respectively, indicating the presence of the methyl ester (OCH_3). This regioselective chlorination and the acyl nucleophilic substitution was recently utilised by Jones in the synthesis of poly(ADP-ribose)polymerase inhibitors for the treatment of cancer.[66]

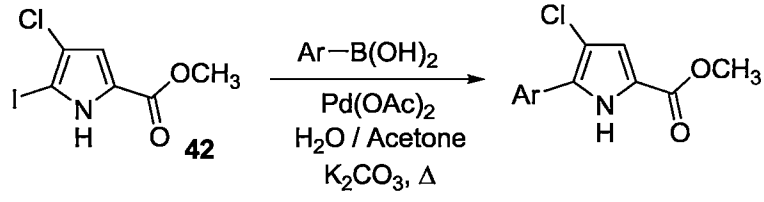


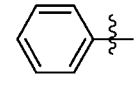
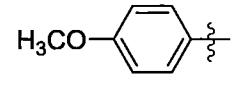
Scheme 18 – Regioselective Halogenation

For the formation of the Suzuki-Miyaura coupling precursor, an iodo group must be introduced to C5 which was affected using the silver promoted iodination as previously described. The desired chloro-iodo substituted pyrrole **42** was obtained

in 86% yield. (Scheme 18) Examination of the ^{1}H NMR spectrum showed the presence of a doublet at 6.80 ppm with a coupling constant of 2.7 Hz, indicating that the only pyrrolic proton that couples to the NH at C3, due to the loss of the pyrrolic proton at C5. Mass spectroscopic data showed molecular ions 285 and 287 gmol^{-1} in a 3:1 ratio, which also indicates the presence of chloride and iodide, hence the formation of the dihalo pyrrole **42**.

This tri-substituted pyrrole **42** was then subjected to the modified ligandless Suzuki-Miyaura coupling reaction. (Scheme 19) The reaction was carried out with 2.5 equivalents of either phenylboronic acid or *p*-methoxyphenyl boronic acid and palladium acetate in acetone and aqueous potassium carbonate for 6 h. The corresponding 4-chloro-5-aryl-substituted pyrroles **66** and **67** were isolated in good yields.

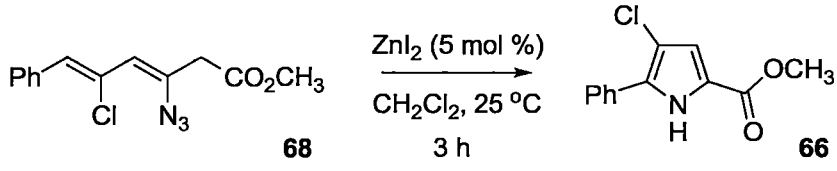


	Ar	%Yield
66		75%
67		82%

Scheme 19 – Formation of C5-Aryl Pyrroles

Examination of the ^{1}H NMR spectrum of compound **62** showed the new resonance at 7.40 and 7.72 ppm which represents the aromatic protons from the phenyl

group, as well as the resonances in the aromatic region in the ^{13}C NMR. The resonance of the pyrrolic proton has also been shifted from 6.80 to 6.91 ppm and is consistent with that reported recently for which was synthesised by cyclisation of dienyl azides **68** using catalytic zinc iodide.[67] (Scheme 20)



Scheme 20 – Formation of C2,4,5-trisubstituted pyrrole

The 5-*p*-methoxyphenyl pyrrole **67** was also characterised with the same key features by spectroscopic analyses. Examination of the ^{1}H NMR spectrum showed two signals of distorted doublets at 6.9 and 7.6 ppm for a typical 1,4-disubstituted aromatic ring. Although the ^{1}H NMR spectrum only showed a singlet at 3.85 ppm, the integration ratio of 6 and the signals at 51.94 and 55.51 ppm in the ^{13}C NMR spectrum confirmed the presence of both methyl groups. Mass spectroscopy showed the molecular ions 265 and 267 $gmol^{-1}$ in a 3:1 ratio, hence the chloride is still present, which confirms the chemoselectivity of the Suzuki-Miyaura cross-coupling.

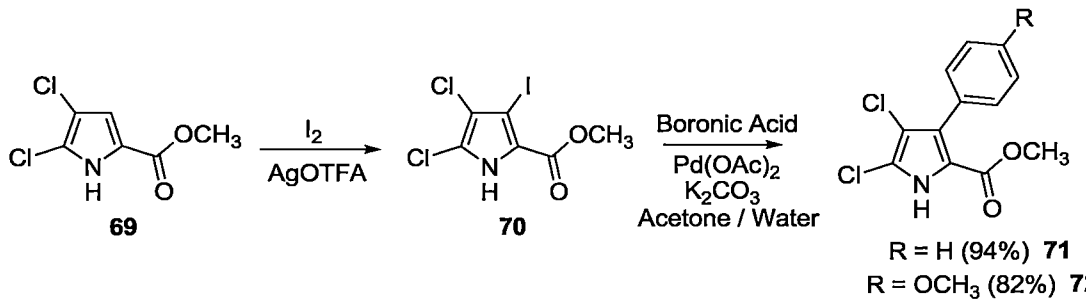
1.2.2 Formation of C3-Aryl Pyrroles

The synthesis of C3-substituted pyrroles followed in a similar manner as the formation of C5-aryl pyrroles. Again, for cross-coupling to take place at C3, iodination must occur at its position. Since both C4 and C5 require blocking, the

stronger electron withdrawing group at C2 is not required. Thus, pyrrole methyl ester **44** reacts with two equivalents of sulfuryl chloride to give the 4,5-dichloro pyrrole **69** in 91% yield. The resonance for the only pyrrolic proton at C3 was shown as a doublet at 6.8 ppm with a coupling constant of 3.0 Hz supporting the chlorination at both C4 and C5. The presence of one singlet at 3.87 ppm in the ^{1}H NMR spectrum was a good indication that only one product was formed. Hence, there was no over-halogenated product present.

This was followed by iodination with I_2 / AgOTFA which gave the tetra-substituted pyrrole **70** as the Suzuki-Miyaura cross-coupling precursor in 77% yield. (Scheme 21) Although the characterisation was difficult due to the lack of distinguishable features, examination of the ^{1}H NMR spectrum showed the loss of the pyrrolic proton and the presence of the ester at 3.92 ppm and the N*H* at 9.72 ppm. The ions at 319, 321 and 323 are in agreement with the two chlorides in the molecule, and which support the formation of the tetrasubstituted pyrrole **70** with molecular formula $C_6H_4Cl_2INO_2$.

The pyrrole **70** was subjected to the Suzuki-Miyaura cross-coupling reaction with both phenyl boronic acid and *p*-methoxyphenyl boronic acid independently, under the described ligandless cross-coupling conditions. (Scheme 21) The corresponding C3-aryl pyrroles were isolated in excellent yields after chromatography.



Scheme 21 – Formation of C3-aryl-pyrrole chlorides

Although there is a lack of distinguishable features of the compound **71**, the ^{1}H NMR spectrum indicated a multiplet at 7.5 ppm with an integration ratio of 5 compared to the peak at 3.73 ppm for the methyl ester. Mass spectroscopy also showed an isotope pattern with molecular ions 269, 271 and 273, consistent with the molecular formula $C_{12}H_9Cl_2NO_2$, supporting the presence of chlorides at C4 and C5.

The 4,5-dichloro-3-*p*-methoxyphenyl pyrrole **72** was also characterised in a similar manner. The *p*-methoxyphenyl group was represented by the multiplets at 6.95 and 7.35 ppm, and the methoxy group as a singlet at 3.83 ppm in the ^{1}H NMR spectrum. Examination of the ^{13}C NMR spectrum also showed the aromatic resonances at ~120 ppm, as well as the new resonance at 55.57 ppm for the methoxy carbon. The ions at 299, 301 and 303 in the mass spectrum also showed the presence of both chlorides. While mass spectroscopy gave the correct molecular formula, the spectroscopic data could not provide confirmation of the position of the aryl group, but fortunately compound **72** was highly crystalline. Therefore, the X-ray crystal structure was obtained which confirmed the formation of the product **72**, and the regioselectivity of the halogenation steps and the selectivity of this ligandless cross-coupling reaction. (Figure 4)

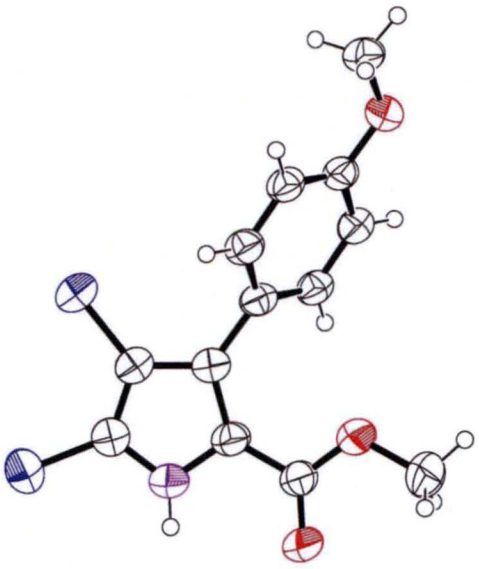
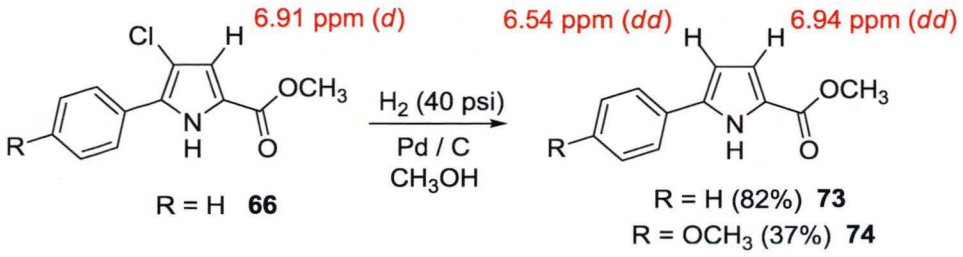


Figure 4 – An ORTEP diagram of compound **72** derived from X-ray crystallographic data (Purple = Nitrogen, Red = Oxygen, Blue = Chlorine)

1.2.3 Reductive Dechlorination

To complete the synthesis of C3- and C5-aryl pyrroles, the chloro groups must be removed. There are several reduction methods which can remove a chloro group. Catalytic hydrogenation is one of the commonly used methods for reductive dechlorination, because it is simple and chemoselective.[48,68,69] Catalytic hydrogenation has the ability to remove chloride from the pyrrole system, and potentially reduced the pyrrole. However, as electron rich pyrroles do not readily undergo catalytic hydrogenation under mild conditions,[70] it was envisioned that chloride reduction would be selective.

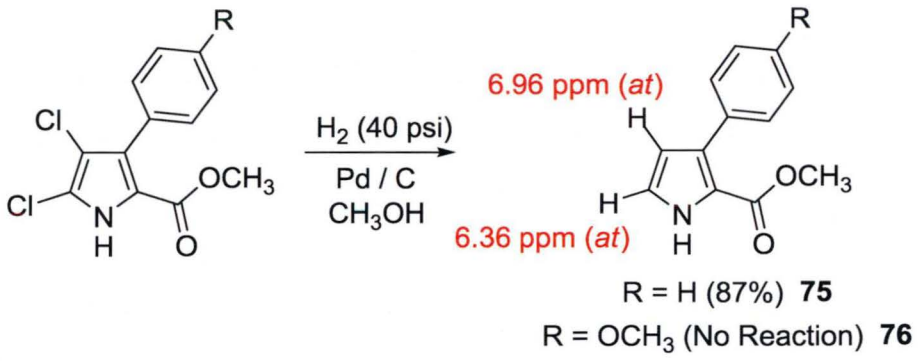


Scheme 22 – Removal of chlorine *via* catalytic hydrogenation

Therefore, 4-chloro-5-phenyl pyrrole **66** was hydrogenated at 40 psi under standard catalytic hydrogenation conditions with palladium on carbon in methanol on a Parr shaker for 6 h.[70] (Scheme 22) After purification by column chromatography, the desired product **73** was isolated in 82% yield. Examination of the ^{1}H NMR spectrum showed two sets of doublet of doublets at 6.96 and 6.54 ppm, confirming the existence of the pyrrolic proton at C3 and C4 respectively. The protons appear as a doublet of doublet due to the coupling to each other, as well as the proton on the nitrogen. The coupling constant of 3.9 Hz is also considered as the pyrrolic protons are adjacent to each other. The spectral data was also consistent with the comparison to the ^{1}H NMR spectrum as reported in literature for compound **73**.[67]

The *p*-methoxy phenyl derivative **67** was also subjected to the standard catalytic hydrogenation conditions and purification by column chromatography on silica gel. The desired product **74** was obtained in 37% yield, as well as 25% of the unreacted starting material **67**. Examination of the ^{1}H NMR spectrum also indicated the key feature of a doublet of doublets at 6.43 ppm representing the pyrrolic proton at C3; that couples to the pyrrolic proton at C4 and to the N*H*, giving a coupling constant of 3.0 and 2.7 Hz respectively. This was consistent to that reported in literature.[67]

It is not clear why reduction was incomplete. However, increased reaction times failed to drive the reaction to completion.



Scheme 23 – Reductive dechlorination *via* catalytic hydrogenation

Since catalytic hydrogenation could readily remove the chloro groups, the C4,5 dichlorinated 3-phenyl pyrrole **71** was also subjected to the standard catalytic hydrogenation conditions. (Scheme 23) Examination of the ^{1}H NMR spectrum suggested the formation of 3-phenyl pyrrole **75** in 87% yield, as the expected doublet of doublets for the two pyrrolic protons at C4 and C5 appeared as apparent triplets at 6.36 and 6.96 ppm indicating the removal of the chloro groups. Mass spectroscopy also confirms the removal of the chlorides with a molecular ion of 201 gmol^{-1} for the product and consistent with the formula $C_{12}H_{11}NO_2$.

Unfortunately, when the 3-*p*-methoxyphenyl derivative **72** was subjected to the standard catalytic hydrogenation, examination of the ^{1}H NMR spectrum of the crude mixture showed only the starting material. It was hypothesised that as the *p*-methoxy group is a good electron donor, the increased electron density of the pyrrole nucleus hinders the reduction of chloride. Therefore, more active catalysts

or vigorous reduction conditions might be required for election rich substrates. This could also explain the incomplete reaction of **67**.

To evaluate different catalysts and conditions, the phenyl derivative was used as the test substrate. For simplicity, the reactions were carried out under a balloon of hydrogenation instead of a Parr shaker. Platinum on carbon (Pt/C), rhodium on alumina (Rh/Al), and palladium hydroxide ($Pd(OH_2)$) were used, as well as acetic acid as a solvent to avoid potential catalyst poisoning. The results are given in the following table. (Table 3) Analysis of the crude product mixture by ^1H NMR spectroscopy revealed that the starting material was returned in all cases. Despite using typically more active catalysts, such as platinum on carbon, rhodium on alumina and palladium hydroxide, palladium on carbon was still the most effective.

S.M.	Catalyst	Solvent	Pressure	Time	Outcome (% yield)
66	Pd/C	MeOH	1atm	16 hr	1:1 (S.M. vs Product)
66	Pt/C	MeOH	1atm	16 hr	N.R.
66	Pt/C	Acetic Acid	1atm	16 hr	N.R.
66	Rh/Al	MeOH	1atm	16 hr	7:3 (S.M. vs Product)
66	$Pd(OH)_2$	MeOH	1atm	16 hr	3:2 (S.M. vs Product)
71	Pt/C	MeOH	1atm	16 hr	3:1 (S.M. vs Product)
72	Pd/C	MeOH:Acetic Acid (10:1)	40 psi[#]	6 hr	N.R.
72	Pt/C	MeOH	40 psi[#]	6 hr	N.R.

*S.M. = Starting Material, N.R. = No Reaction, [#]Reaction conditions as per previously discussed.

Table 3 – Summary of results from catalytic hydrogenation

Even the addition of acetic acid to methanol, in a Parr shaker hydrogenator did not give any dechlorination for the unreactive dichloride **72**. As such, to facilitate the dechlorination of the electron rich aryl-pyrroles, other dissolving metal chemistry was considered. i.e. radical mediated tri-*n*-butyltin hydride reduction,[71] copper hydride reduction[72] and zinc / acid reduction.[73] Chloro-pyrroles were treated under the reported conditions, but only starting material and/or decomposition was observed. Due to limited material, no further investigations were carried out. Nevertheless, the reduction with palladium on carbon has proved the methodology sound. However, further research is required for the dechlorination of the electron rich substrates.

1.3 Conclusion

In this chapter, a general regioselective synthetic pathway was developed for C3, C4, and C5 aryl pyrrole-2-carboxylates, exploiting different rates for the reaction of halides. This pathway has demonstrated the effective syntheses of a number of representative examples, and can be extended and applied towards other mono- and diaryl-pyrrole containing natural products. This is illustrated in the synthetic pathway for the synthesis of lamellarin derivatives, which will be discussed in the following chapter.

Chapter 2

Formation of Lamellarins and Diarylated Pyrroles

2.1 Synthesis of Lamellarin Q Dimethyl Ether

As previously mentioned, many natural products have structures containing a biaryl-substiuted pyrrole, such as the lamellarins. (Figure 1) In the previous chapter, the synthesis of aryl substituted pyrroles demonstrated two key features, regioselective halogenation with chloride employed as a blocking group, and the ligandless Suzuki-Miyaura cross-coupling. This ligandless palladium-mediated coupling was shown to be effective for the introduction of an aryl group onto an electron rich pyrrole. This chapter will utilise these methods and extend the protocol towards the regioselective synthesis of diaryl-substituted pyrroles.

Lamellarin Q (**80**) is a pyrrole that consists of two *p*-hydroxyphenyl groups at C3 and C4, as well as a methyl ester at C2. Therefore, the aryl groups can be introduced at C3 and C4 *via* the regioselective halogenation, followed by the ligandless Suzuki-Miyaura cross-coupling reaction. Since the ligandless cross-coupling reacts more rapidly with iodide, iodides must be affixed at C3 and C4. As demonstrated previously, when C4 is occupied on a pyrrole, the next reactive position is C5. In order to form a 3,4 diiodo pyrrole **78**, C5 must be masked with a chloride. Hence, the order of halogenation requires iodination, chlorination followed by a second iodination which completes the tetrasubstituted coupling precursor. (Scheme 24)

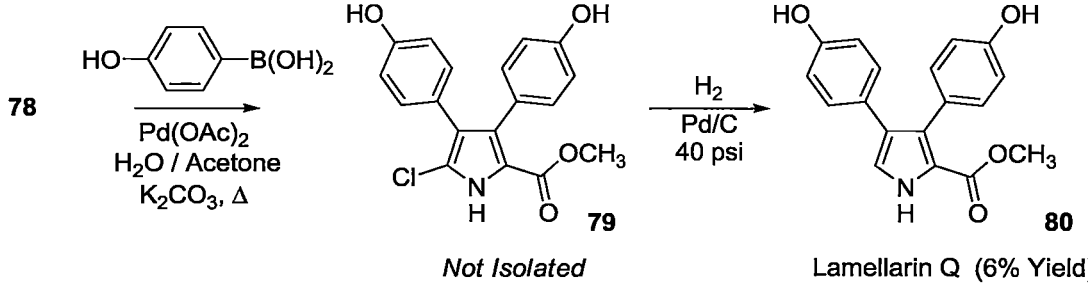
Scheme 24 – Selective halogenation

As a result, the 4-iodo pyrrole **58** was reacted with one equivalent of sulfuryl chloride to give the dihalo pyrrole **77** in 84% yield. The formation of the product **77** was supported by the loss of the C5 pyrrolic proton at 7.01 ppm in ^{1}H NMR for the precursor **58**. The remaining pyrrolic proton at C3 resonates as a doublet at 6.94 ppm due to the coupling to the N*H* (coupling constant 2.7 Hz) indicating only one remaining hydrogen on the pyrrole ring. The presence of the chloride was supported by mass spectrometry which shows molecular ions at 285 and 287 in a 3:1 ratio.

The intermediate **77** was then iodinated with I_2 / AgOTFA to form the desired 3,4-diiodo pyrrole **78**. Although there is a lack of distinguishable features, examination of the ^{1}H NMR spectrum indicated a loss of pyrrolic proton at 6.94 ppm for the precursor. The methyl ester also shifted slightly from 3.86 to 3.91 ppm. The molecular ions 411 and 413 in a 3:1 ratio also suggested the presence of two iodides and a chloride within the structure.

The modified ligandless Suzuki-Miyaura cross coupling reaction was shown to be effective for these pyrrole systems. With the corresponding diiodo **78**, biarylation was possible. Lamellarin Q has two *p*-hydroxyphenyl groups at C3 and 4, hence

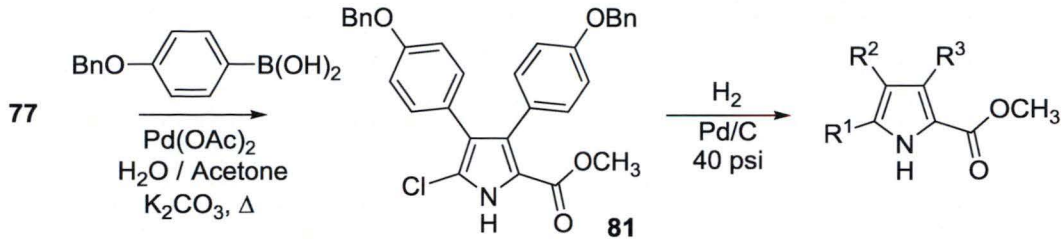
p-hydroxyphenyl boronic acid was considered for the first attempt to avoid protecting group chemistry. Therefore, pyrrole **78** was subjected to the modified ligandless Suzuki-Miyaura coupling reaction described previously with *p*-hydroxyphenyl boronic acid. (Scheme 25) The reaction was monitored by TLC, however the progress of the reaction was not clear on completion, since there was no change of R_f for the major component. Therefore it was difficult to determine. Analysis of the ^1H NMR spectrum of the crude reaction mixture is not conclusive as there is no identifying proton to observe. Therefore, the crude Suzuki-Miyaura pyrrole was subjected to catalytic hydrogenation under the standard conditions for further confirmation of a successful reaction. After column chromatography, the desired product lamellarin Q (**80**) was obtained and consistent with the reported spectral data.[74] Examination of the ^1H NMR spectrum showed the resonance in the aromatic region at 6.75, 6.78, 6.95 and 7.07 ppm for the eight aromatic protons, and a doublet at 7.12 ppm representing the pyrrolic proton at C5. However, the yield of lamellarin Q (**80**) was only 6% over the two steps. It was not clear if the low yield was caused from incomplete cross-coupling or reduction. We anticipate a hindrance to the reduction due to the increased electron density of the pyrrole ring by the hydroxyl groups.

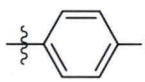
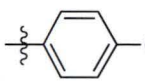
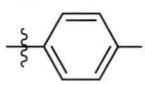
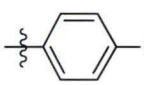
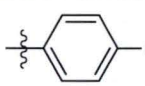
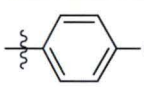
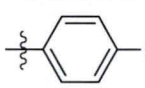
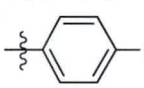
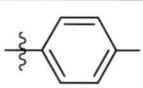
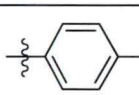


Scheme 25 – Synthesis of Lamellarin Q

Polyphenyolics are well known to be problematic in many synthetic schemes and often requiring protection.[75] One of the commonly used protecting groups for phenols is the benzyl group (Bn). They are commonly used because they can be easily removed under standard catalytic hydrogenation. In theory, 4-benzyloxyphenyl boronic acid could be used on the chloro pyrrole, which then undergoes catalytic hydrogenation. This could remove both the protecting and blocking groups, at the same time yielding the product lamellarin Q.

In order to test this hypothesis, the diiodo pyrrole **78** was reacted with *p*-benzyloxyphenyl boronic acid under the same ligandless Suzuki-Miyaura coupling conditions. (Scheme 25) After attempted purification by column chromatography, examination of the ^{1}H NMR spectrum showed a complex mixture as indicated by the methine protons from the benzyl groups. Unfortunately, no pure compound could be isolated despite many attempts to recrystallise the crude mixture. The lack of pyrrolic protons made any characterisation difficult. As a result, the most promising mixture as indicated by ^{1}H NMR spectroscopy underwent high pressure catalytic hydrogenation with palladium on carbon in order to remove the protecting and blocking groups. It was difficult to determine if lamellarin Q was formed by analysis of the ^{1}H NMR spectrum due to overlapping signals. Therefore, the crude mixture was analysed by mass spectrometry.



	R^1	R^2	R^3	MS
81	Cl			523 : 525 (3:1)
82	H			489
83	H			$[M-H]^+$ = 398
79	Cl			343 : 345 (3:1)
80	H			309

Scheme 26 – Deprotection

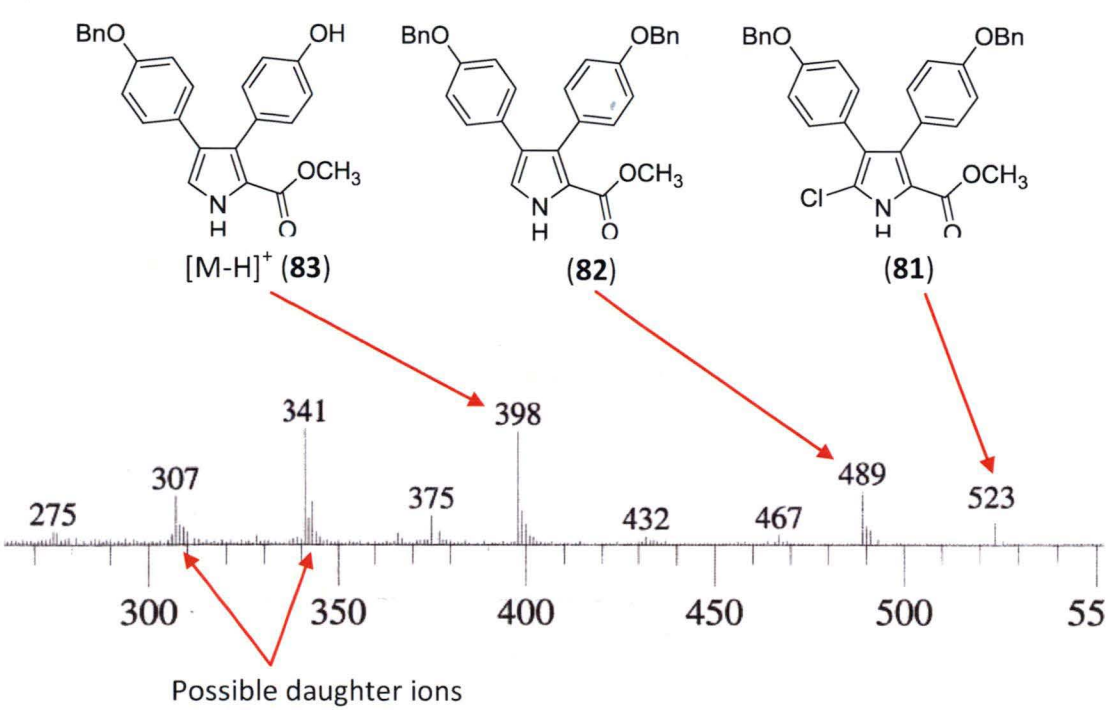


Figure 5 – Mass spectroscopic analysis for Scheme 25

The spectrum as shown above has indicated a mixture of compounds present including compound **81**, **82**, and **83**. (Figure 5) Mass spectroscopic data indicated molecular ions at 523 and 525 in 3:1 ratio suggesting the presence of the Suzuki-Miyaura product **81**. Compound **82** suggested the presence of molecular ion 489, indicating the loss of chloride at C5. The presence of compound **83** was also indicated as a $[M-H]^+$ ion at 398 showing the loss of one benzyl group at either C3 or C4. Compound **79** and lamellarin Q (**80**) could also be present, and they could potentially be daughter ions of compound **81**. These results clearly indicate that the catalytic hydrogenation did not go to completion, with a mixture of partial removal of protecting and blocking groups. Even with the extended times, complete deprotection was not achieved. Whilst this was not surprising for the chloride, it was not expected for the deprotection of the benzyl ether.

Recent research has shown many synthetic approaches utilise the Fürstner intermediate **22** as a key intermediate to prepare lamellarins and derivatives.[76,77] This intermediate is also only a few steps away from the total synthesis of many naturally occurring products, such as lukianol A (**5**)[76] and ningalin B (**6**).[32] This intermediate **22** has two methoxy groups instead of two hydroxyl groups attached to the phenyl rings.

Despite the reduction problem encountered previously, methoxy derivatives are much easier to handle, more stable and if required can be converted to the free phenol. Therefore, this synthesis of the Fürstner intermediate was examined. The diiodo pyrrole **78** was reacted with 2.75 equivalents of *p*-methoxyphenyl boronic

acid under the previously described ligandless Suzuki-Miyaura coupling conditions. (Scheme 27) Ultimately, after purification by column chromatography, a single product was isolated to yield the chlorinated lamellarin Q dimethyl ether **84** in 45% yield. Examination of the ^{1}H NMR spectrum showed two new signals at 3.74 and 3.77 ppm, each with an integral of 3 representing the two new methoxy (OCH_3) groups. The existence of multiplets in the aromatic region shows the presence of eight aromatic protons. Mass spectroscopy showed molecular ions at 371 and 373 in a 3:1 ratio, indicating the presence of the chloride. This chlorinated lamellarin Q dimethyl ether is also highly crystalline and recrystallised from dichloromethane / hexanes which allowed a single crystal X-ray analysis to be carried out. The structure was obtained and is shown in the following ORTEP diagram, confirming the formation of compound **84**. (Figure 6) This also confirms the order of halogenation at C4, C5 then C3, and the chemoselective cross-coupling reaction.

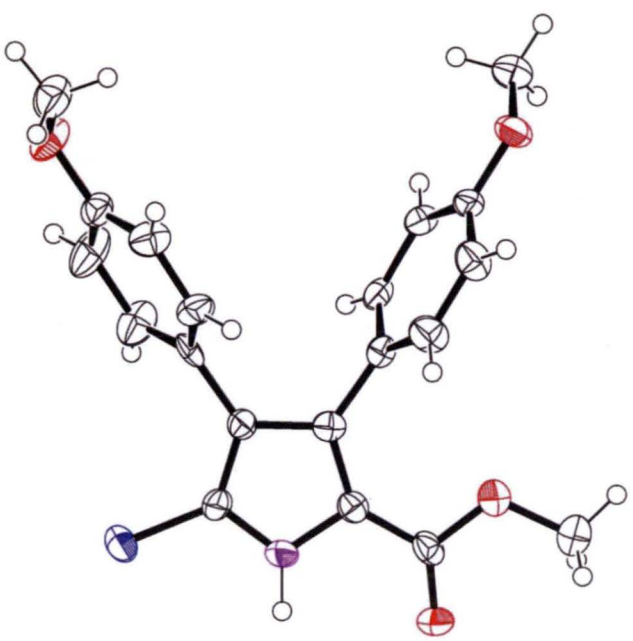
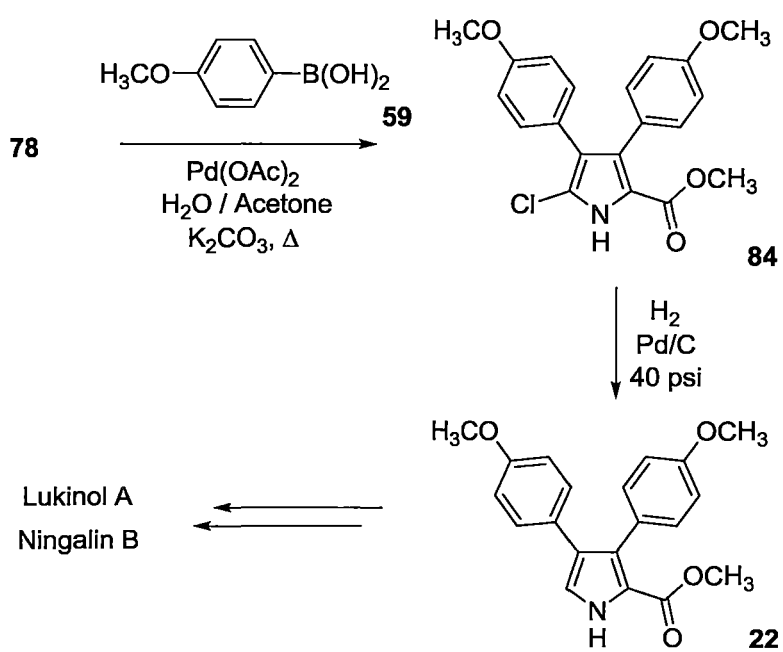


Figure 6 – An ORTEP diagram of compound **84** derived from X-ray crystallographic data (Purple = Nitrogen, Red = Oxygen, Blue = Chlorine)

The final step in the synthesis of the Fürstner intermediate, lamellarin Q dimethyl ether (**22**) was reductive dechlorination *via* catalytic hydrogenation. As reported in the previous chapter, *p*-methoxy substrates can be problematic when undergoing catalytic hydrogenation; nevertheless the intermediate was subjected to catalytic hydrogenation using palladium on carbon. (Scheme 27) Examination of the ^{1}H NMR spectrum indicated three sets of apparent doublets at 6.75, 6.84 and 7.19 ppm, each of these representing two aromatic protons from the 1,4 disubstituted phenyl groups. The fourth set of the aromatic protons appears as a multiplet at 7.03 ppm with an integration ratio of 3, as they overlap with the pyrrolic proton at C5. The spectral data was consistent with that reported in literature,[78] and confirms the formation of Lamellarin Q dimethyl ether (**22**) in 72% yield. Surprisingly the yield for dechlorination was very high for this instance compared to other electron rich substrates.



Scheme 27 – Synthesis of Lamellarin Q dimethyl ether

The synthesis of lamellarin Q dimethyl ether was successfully developed and has been communicated.[48] The synthetic methodology developed provides regio and chemoselective control, utilising halides for activation and as blocking groups, in conjunction with the ligandless Suzuki-Miyaura cross-coupling reaction where lamellarin Q dimethyl ether was formed in good yield. Lamellarin Q dimethy ether has been shown previously transformed to lukinol A in three steps, which completes a formal synthesis of this natural product.[26]

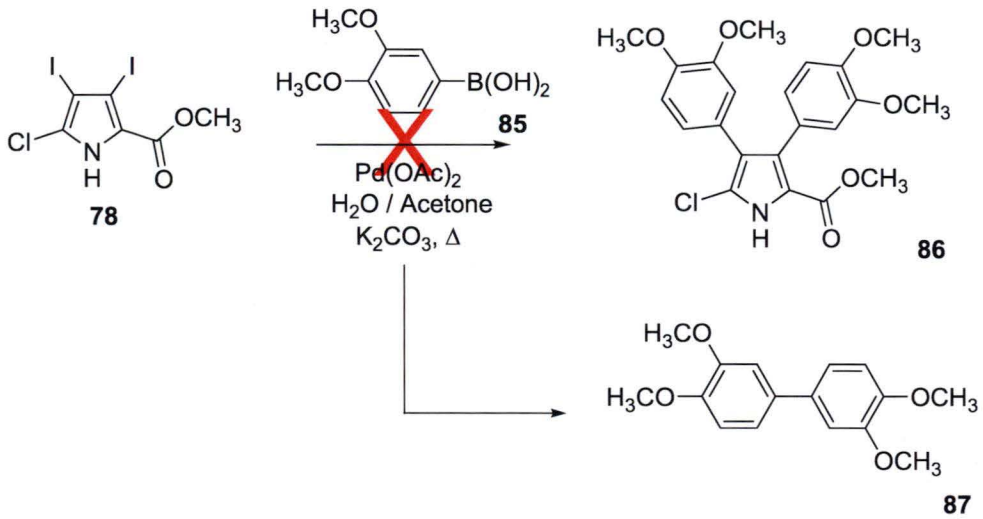
2.2 Other Biarylations

2.2.1 3,4 Biarylations

The corresponding regioselective halogenation of pyrroles allowed the controlled synthesis of arylpyrroles *via* ligandless cross-coupling, taking advantage of this effective synthetic pathway. Therefore derivatives of lamellarin Q were also investigated. Many derivatives in the lamellarin family contain several methoxy groups on the aryl substituents, therefore the 3,4-dimethoxy derivative of lamellarin Q dimethyl ether was targeted due to the commercial availability of the corresponding boronic acid **85**. Hence the cross-coupling of the boronic acid and diiodo pyrrole **78** was conducted under the ligandless cross-coupling conditions. (Scheme 28) Unfortunately, TLC and ^{1}H NMR spectroscopy showed a complex mixture of products. On chromatography, the target compound could not be isolated but two promising identified fractions were subjected to further analysis, as indicated by ^{1}H NMR spectroscopy. The first major fraction was submitted for high resolution mass spectrometry analysis. A trace of the target compound **86** was

observed by the presence of ion at 431. The major ions at 329 and 331 with a ratio of 3:2 indicated the pattern expected for the presence of 2 chlorides. Therefore, this suggests that some halide scrambling may have occurred. This was unexpected and has not been observed previously.

The second fraction crystallised and was identified as the biphenyl by-product **87**. Examination of the ^{1}H NMR spectrum of **87** indicated the multipets at 9.6 ppm for the six aromatic pyrroles, and four singlets at 3.86, 3.88, 3.89 and 3.93 ppm representing the four methoxy OC*H*$_3$ peaks. X-Ray crystallography confirmed the formation of the biphenyl, and appears to be a major reaction pathway. This finding was not unexpected due to the protodeboronation as discussed previously.



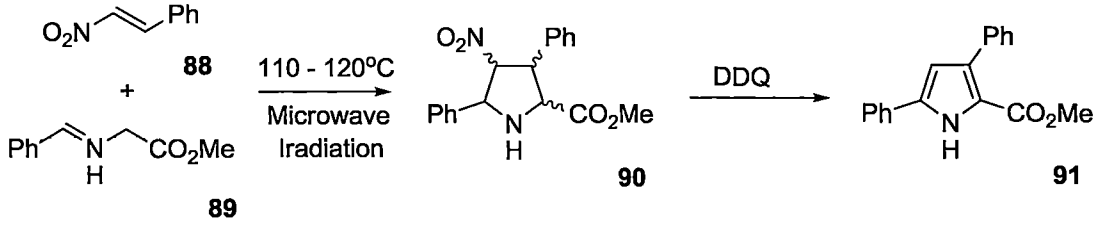
Scheme 28 – Biarylation

Previously, the biarylations of the ligandless cross-coupling conditions were shown to be effective for these electron rich pyrrole systems. However this was not the case for these electron rich poly-methoxyphenyl substrates. It would be expected

that the cross coupling could be effected with other catalyst systems, but that was outside the interest of the project, so no further investigations were undertaken.

2.2.2 3,5 Biarylations

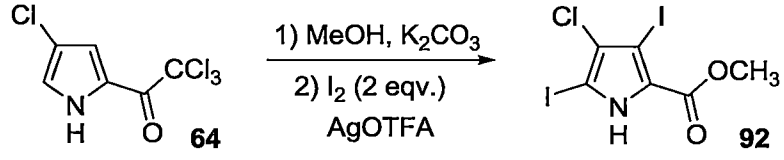
3,5 Diaryl-pyrroles have been synthesised in the development of anticonvulsants and possess other important biological activity.[79,80] Most syntheses of these biaryl pyrroles are by cyclisation methods to form the pyrrole core with the substiutuents in place.[79,81,82] For example Cossio *et al.* recently reported the use of microwave radiation to thermally isomerise α-amino ester derived imines **88** to their corresponding azomethine ylides, and subsequent 1,3 dipolar cycloaddition with nitrostyrene **89** to give nitropyrrolidine **90** which underwent oxidation with DDQ to yield 3,5 diaryl pyrrole derivatives **91**.[79] (Scheme 29)



Scheme 29 – Formation of 3,5-diaryl pyrroles *via* azomethine cycloaddition / oxidation

Despite the commonly used cyclisation, Handy also demonstrated a one-pot Suzuki-Miyaura cross coupling method as previously mentioned.[42] So we also approached the synthesis of 3,5 bi-arylated pyrrole-2-carboxylated using our developed methodology. In this synthetic pathway, chloride was placed at the most reactive

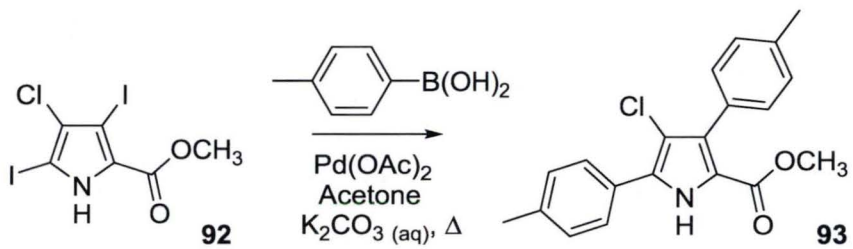
C4 with the use of the strongly electron withdrawing, trichloromethyl ketone at the 2 position of the pyrrole. This intermediate was then converted to methyl-4-chloropyrrole-2-carboxylate (**64**) utilising the haloform reaction in excellent yields as with previous examples. As the target compound consists of two aryl groups at C3 and 5, iodides are required at both of these positions for the Suzuki-Miyaura cross-coupling. Therefore the reaction of **65** with two equivalents of iodine and AgOTFA gave the desired Suzuki-Miyaura coupling precursor **92** in 68% yield. (Scheme 30) Although characterisation was again difficult due to the lack of distinguishable features in the ^{1}H NMR spectrum, the loss of the pyrrolic protons at 6.80 and 6.91 ppm indicating the formation of the tetra-substituted pyrrole **92.**



Scheme 30 – Regioselective halogenation

Due to the problems observed in the dechlorination of electron rich pyrroles, we decided to avoid *p*-methoxyaryl derivatives as it would increase the electron density and potentially cause problems. Therefore, *p*-tolyl group was used as the substituent because the methyl group on the tolyl derivative could be used as a marker for NMR analysis. *p*-Tolyl boronic acid was reacted with diiodo pyrrole **92** and underwent the optimised Suzuki-Miyaura coupling conditions, to give methyl 4-chloro-3,5-ditolyl pyrrole **93** in 78% yield after purification by column chromatography. (Scheme 31) ^{1}H NMR spectroscopic analysis showed three singlets resonating at 2.34, 2.41 and 3.73 ppm indicating the two methyl groups

from the tolyl group and the methyl ester (OCH_3), respectively. Mass spectrometry also gave the correct molecular ions 339 and 341 in a 3:1 ratio, indicating the presence of chloride. The compound was highly crystalline and a crystal of suitable quality was obtained for X-ray crystal structure with the result shown in the following ORTEP diagram.[83] (Figure 7) Once again, the regioselective halogenation was confirmed, as was the selectivity of the Suzuki-Miyaura cross-coupling.



Scheme 31 – 3,5-Biarylation

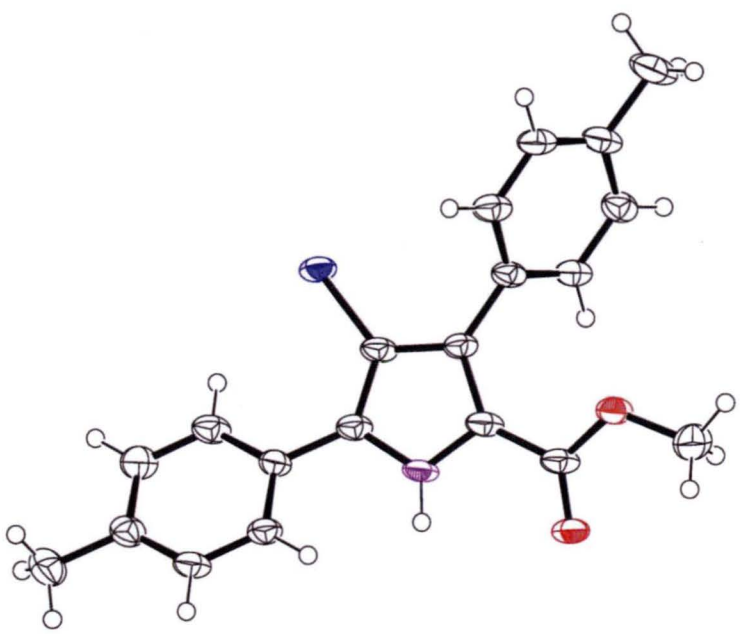
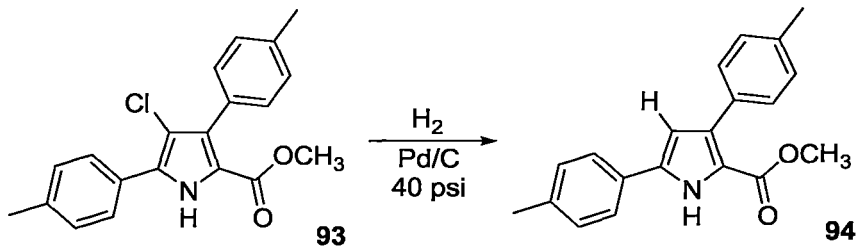


Figure 7 – An ORTEP diagram of compound **93** derived from X-ray crystallographic data (Purple = Nitrogen, Red = Oxygen, Blue = Chlorine)

To obtain the 3,5-diaryl pyrrole, dechlorination was required. However, reductive dechlorination of this pyrrole derivative was more difficult than expected. Subjecting the chlorinated pyrrole **93** to catalytic hydrogenation under the standard conditions with palladium on carbon, (Scheme 32) showed only unreacted starting material by the analysis of the ^{1}H NMR spectrum. (Entry 1) Due to the lack of solubility of the chlorinated pyrrole in methanol, which we thought maybe one cause for this lack of reaction, ethyl acetate was added to enhance solubility. This had some effect as the desired product **94** was observed in ~5% yield. (Entry 2) Examination of the ^{1}H NMR spectrum of the crude mixture showed a signal resonated at 6.5 ppm representing the pyrrolic proton at C4. The percentage yield was determined by the comparison of two resonances for the methyl ester at 3.73 and 3.71 ppm. Unfortunately the product was inseparable from the starting material by column chromatography. This initial condition of the reaction increased the reaction time to 8 h, but no improvement was observed. Other catalysts, such as platinum on carbon and palladium dioxide were ineffective for dechlorination in this system.

This substrate was also briefly examined with dissolving metal reduction conditions such as zinc in acidic conditions. Refluxing compound **93** in acetic acid with zinc powder gave only decomposition. Zn / HCl was also used, one of the harsher reduction methods to create a high flux of electrons. However, this also failed.



Entry	Conditions	Results
1	Pd/C, MeOH, H_2 (40psi), 6 h	S.M.
2	Pd/C, MeOH : ethyl acetate (1:1), H_2 (40psi) 8 h	95: 5 (S.M. : Product)
3	Pt/C, MeOH : ethyl acetate (1:1), H_2 (40psi), 6 h	S.M.
4	$Pd(OH)_2$, MeOH, H_2 (1 atm), 16 h	S.M.

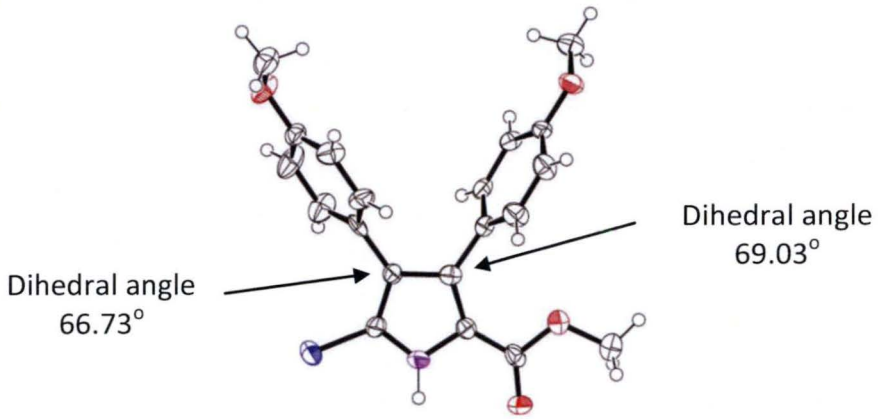
* S.M. = Starting material

Scheme 32 – Reductive dechlorination

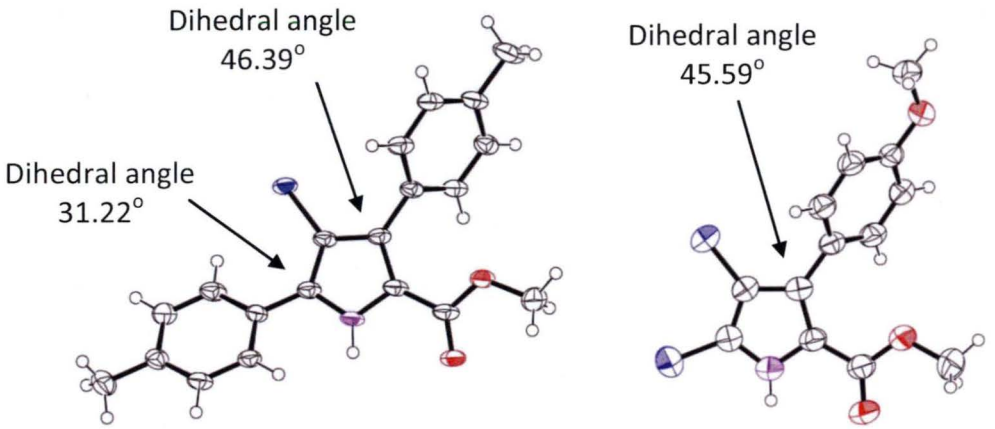
Assuming that it is an electronic effect that hinders the reduction of the chloride, we considered adding an electron withdrawing group, such as Boc on the nitrogen in order to reduce the electron density, to enhance the reduction. Unfortunately, when **93** reacted with Boc anhydride (Boc_2O) in the presence of 4-dimethylaminopyridine (DMAP) under standard conditions,[84] examination of the ^1H NMR spectrum of the crude mixture only indicated the starting material. It is postulated that this reaction failed due to the steric bulk of the C2-C5 disubstituted pyrrole which is possible as examination of the X-ray crystal structure.

It was reported earlier that the 5-chloro-3,4-di-*p*-methoxyphenylpyrrole-2-carboxylate (**84**) could undergo catalytic hydrogenation for dechlorination, whereas

the 4,5-dichloro-3-*p*-methoxyphenylpyrrole-2-carboxylate (**72**) and the 3,5-ditolylpyrrole-2-carboxylate (**93**) showed a lack of reactivity. Therefore, examinations of the X-ray crystal structures were revisited and are shown in figure 8. A difference was observed between the substrate that reacts versus the two that do not. It was noted that the dihedral angle between the phenyl rings and the pyrrole rings for compounds **84**, **72** and **93** differed. The dihedral angle for compound **84** is much greater than for compounds **93** and **72**. It is speculated for compound **84** (dihedral angle = 66.73° and 69.03°), that because of the phenyl groups not being planar with the pyrrole ring, electron donation *via* resonance into the pyrrole nucleus is limited. This is due to the limited overlap of the p-orbitals of the adjoining pyrrole and phenyl carbon atoms. For compounds **93** and **72**, the smaller dihedral angles between the phenyl and pyrrole rings allow greater resonance electron donation towards the pyrrole nucleus, as the p-orbitals have greater overlap. However, this theory is based only on the analysis of the crystal structures which may not represent the most stable conformation in solution. Further investigation could involve computational analysis of the distribution of electron density of the carbon atom within these compounds and may help provide further evidence for this hypothesis.



Compound **84** (Dechlorination – Successful)



Compound **93**
(Dechlorination - Failed)

Compound **72**
(Dechlorination - Failed)

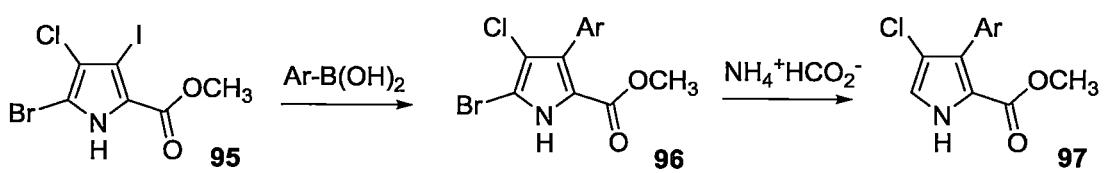
Figure 8 – Comparisons of the dihedral angles of crystal structures **84**, **93** and **72**

2.3 Conclusion

In conclusion, it was demonstrated that the regio and chemoselective modifications of pyrroles, using an iodo group as a cross-coupling activator and a chloro group as a blocking group, in cooperation with the modified ligandless Suzuki-Miyaura cross-

coupling reaction, could be used to synthesise a variety of mono- and diaryl substituted pyrroles in good yield. More importantly, this pathway was employed to develop an alternate synthesis of pyrrole-containing natural products, such as lamellarins including lamellarin Q and its dimethyl ether.

For future work, the lack of reactivity for the dechlorination could be overcome by the replacement of the chloro group with a bromo group. In theory, this should still be selective for the Suzuki-Miyaura cross-coupling. The reduction of the bromide will be much more effective. The bromide could also be used for further cross-coupling, potentially in one-pot, by adding a second boronic acid. Or it could also be reduced in-situ by the addition of a reducing agent, such as ammonium formate.[85] (Scheme 33)



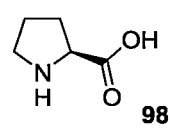
Scheme 33 – Future Work

Part II

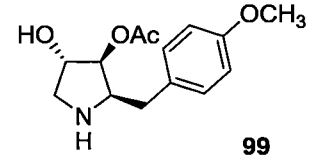
Reduction of Pyrroles

Introduction

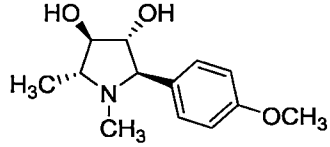
Many saturated five-membered nitrogen-containing heterocycles natural products, such as anisomycin (**99**), codonoposinine (**100**) and preussin (**101**) have been isolated and exhibited useful biological activities. Anisomycin (**99**) is a simple tri-substituted pyrrolidine that was isolated from *Streptomcyces griseolus*, and possesses antibiotic activity against several strains of fungi.[3] Codonoposinine (**100**) is a penta-substituted pyrrolidine which was isolated from *Codonopsis clematidea* and is an antihypertensive agent that does not affect the central nervous system.[4] Preussin (**101**) was isolated from the fermentation broths of *Aspergillus ochraceus* and *Preussia sp*. This structurally novel pyrrolidine alkaloid contain a C9 side-chain and has broad spectrum antifungal activity against both filamentous fungi and yeasts.[5] Recently, the structurally related pyrrolidine alkaloids with the motif of 3,4-dihydroxy-pyrrolidine **102** were isolated from the leaves of bluebells. This was the first identification of **102** in British flora.[86] These compounds are aza-sugars and many show potent activity as glycosidase inhibitors. Due to their interesting biological activities, these compounds and their structural analogues have become popular synthetic targets.



98



99



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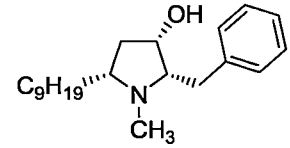

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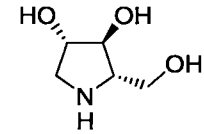
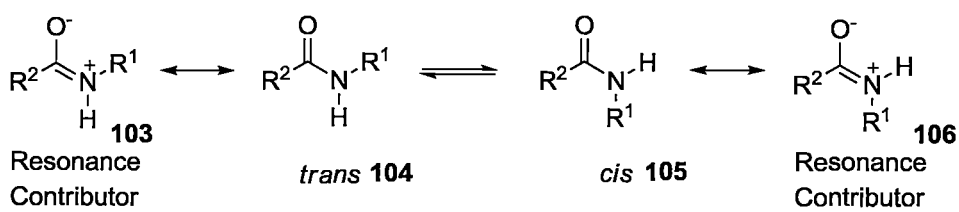


102

The cyclic amino acid proline (**98**) is also a pyrrolidine and is extremely important in synthesis and biology. Proline is one of the 23 amino acids, and known as a β-turn inducer[87] as proline forms *cis*-amides **106** with other amino acids when it is introduced into a peptide chain. It induces a turn in the peptide chain folding back along itself, and is known as a β-turn.[87] (Figure 9) The amide group can exist in either *trans* or *cis* confirmation due to the electronic effects of amide formation. However, due to the resonance contribution of the amides, the rotation of the C-N bond is restricted. (Scheme 34) Therefore, proline plays a key role in controlling the secondary structure of a peptide and ultimately the overall tertiary structure.[87] These events include interactions between peptide hormones and their receptors, antibodies and antigens, regulatory enzymes and their corresponding substrates.[88] HIV-antigens are such an example.[89,90]



Scheme 34 – Resonance contribution of amides

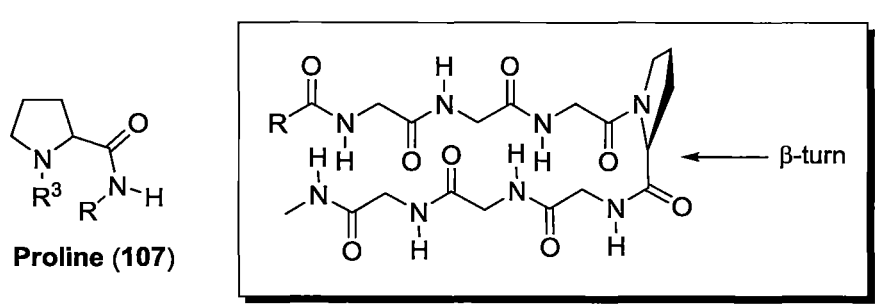
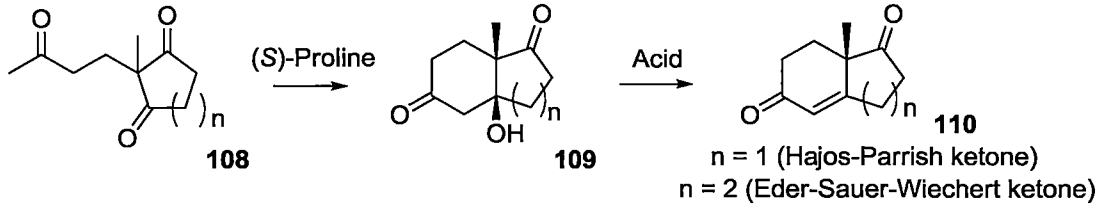


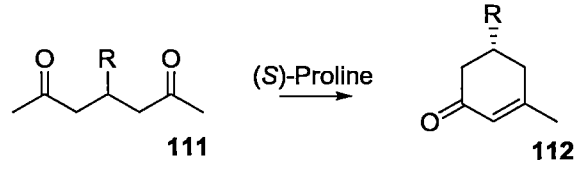
Figure 9 – Proline as a β-Turn

Applications towards organic synthesis

Despite the biological applications, prolines and proline derived compounds have proven to be useful as organocatalysis and chiral scaffolds in organic synthesis. For example, proline can also be a powerful tool in aldol reactions generating new C-C bonds. Hajos-Parrish and Eder-Sauer-Wiechert developed a (-)-proline-catalysed intramolecular aldol reaction in the early 1970s.[91,92] (Scheme 35) Later in the 1980s, Agami demonstrated an asymmetric intramolecular aldol cyclisation of achiral diketones to form cyclohexenes catalysed by proline.[69] (Scheme 36) The key step to these reactions is the utilization of proline to direct asymmetric aldol reactions between two different carbonyl groups yielding enantioselective aldol products. It has been suggested that the mechanism is very complex with more than one proline molecule required, but the formation of a chiral enamine is a key feature.[91,92]

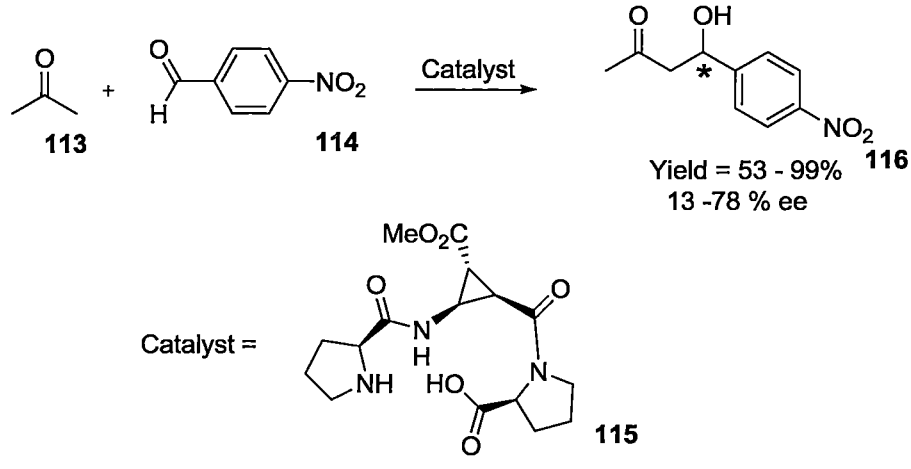


Scheme 35 – Proline catalyses Intramolecular aldol reaction



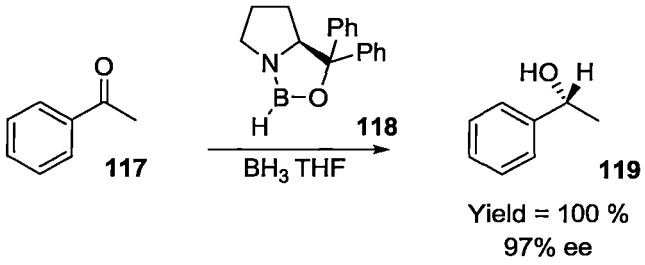
Scheme 36 – Asymmetric intramolecular aldol cyclisation

To date, Reiser's group reported that the proline-containing tri-peptide **115**, containing a conformationally restricted cyclopropane unit and including two turn-inducing elements, is an efficient catalyst for inter and intramolecular aldol reactions. This catalytic system was found to be highly selective with ee ranging from 13% to 78%. The product was obtained in 53% to 99% yields.[93] (Scheme 37)



Scheme 37 - Short peptide-catalysed intermolecular aldol reaction (*Chiral centre)

Proline derived compounds, such as **118** have also been applied to highly enantioselective borane reduction of ketones. In the late 1980s, Corey and co-workers developed the Corey-Bakshi-Shibata (CBS) catalyst, which is formed by the conversion of the carboxylate proline to a tertiary alcohol *via* phenyl Grignard reagent. The catalyst has been used in the reduction of ketones with BH_3.THF complex to give secondary alcohols in good yield with 97 % ee.[94,95] (Scheme 38)

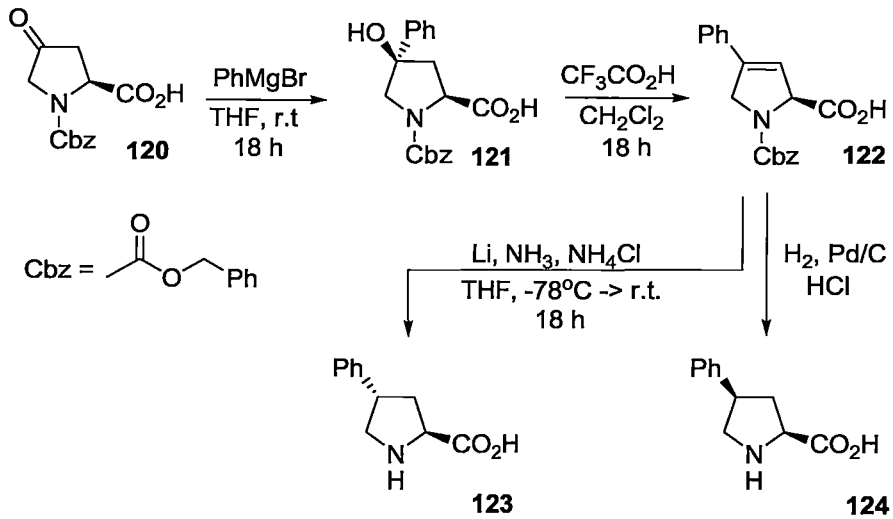


Scheme 38 – Ketone reduction using CBS-catalyst

Diphenyl prolines and analogues have been used as a catalyst for numerous asymmetric transformations which highlight the importance of these systems.

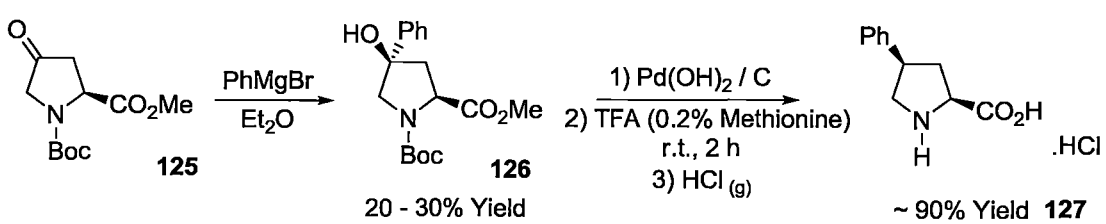
Formation of Proline analogues

Proline derived compounds are useful for biological and medicinal chemistry, as substituents on the ring can have different properties to those of the parent prolines. However, the syntheses towards analogues of this type can be complicated as no general method exists. However, the availability of 4-hydroxy proline means that it has been used extensively as a precursor for other 4-substituted proline derivatives. For example, Petrillo's group reported that 4-hydroxy proline can be used as a template for the synthesis of C4-phenyl prolines.[96] 4-Hydroxyproline was oxidised to 4-oxopyrrolidine **120**, and the phenyl substituent was introduced using a Grignard reagent. Elimination of water gave pyrroline **122** as a key intermediate. As reduction occurred using lithium / liquid ammonia or catalytic hydrogenation the *trans* **123** or *cis* **124** proline derivatives were yielded respectively. (Scheme 39)



Scheme 39 – Synthesis of 4-phenyl-prolines

Hruby's group also reported a similar approach for *cis*-4-aryl-prolines *via* hydrogenolysis of the related intermediate alcohol. (Scheme 40) Grignard reaction of **125** gave the initial *trans*-4-phenyl-Boc derivative **126** and catalytic hydrogenation with palladium hydroxide on carbon under acidic conditions gave the desired *cis*-proline **127** in good yield.[97]

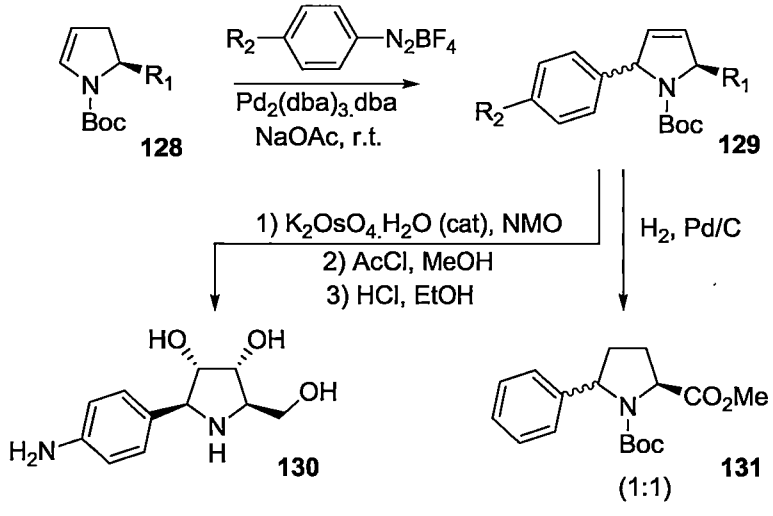


Scheme 40 – Synthesis of 4-*cis*-phenyl-proline *via* hydrogenolysis

C3 and C5-Substituted Prolines

4-Substituted prolines are challenging to synthesise, despite a ready template in 4-hydroxy proline. The syntheses of C5 and C3 substituted prolines have also

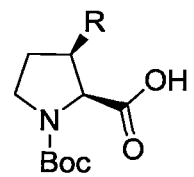
proven to be even more challenging as often they require the synthesis of the heterocycle as well. For example, Correia and co-workers established that C5-aryl prolines can be obtained from 2-pyrrolidine **128**, which was derived from L-pyroglutamic acid.[98] (Scheme 41) The reaction with aryldiazonium tetrafluoroborates *via* Heck arylation gave a mixture of two diastereomeric 2,5-disubstituted prolines **129**. This intermediate was exploited in two ways. Hydrogenation of the alkene, gave a 1:1 mixture of diasteromers of C5-phenyl-proline esters **131** in a low yield. The alternative route involved dihydroxylation of the alkene, followed by reduction of the ester to give rapid access to the aza-sugar **130**, which has shown promising trypanosomal activity, in overall yield of 37% from the pyrroline **129**.



Scheme 41 – Synthesis towards pyrrolidines *via* Heck arylations

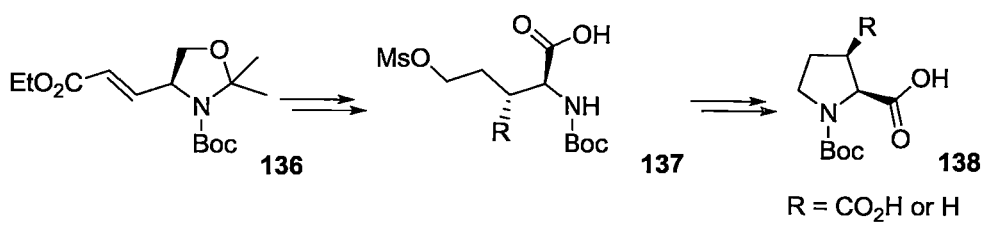
C3-substituted prolines are one of the most examined proline derivatives for peptide modifications. Depending upon the substituents, 3-substituted prolines are conformationally constrained analogues of the cyclic amino acids, such as phenlyalanine **132**, norleucine **133** and aspartate **144**.[99] These 3-substiuted prolines

are the most interesting and useful examples of proline, because the substituents play an important role on the angle of the β-turn within the peptide chains. They are also the most challenging targets. This *cis* isomer adds an extra level of difficulty, as they are not as thermodynamically stable as the corresponding *trans*-isomers. Hence, only a few methods have been reported on the synthesis of *cis*-3-substituted prolines.



R = Ph (**132**)
R = $CH_2CH_2CH_3$ (**133**)
R = CO_2H (**134**)
R = CH_3 (**135**)

Sasaki's group reported the conjugate addition of the α,β-unsaturated ester **136**, with a series of organocuprates, reductions of the ester, mesylation, Jones' oxidation and cyclisation to yield the *cis*-5-substituted proline derivatives **138** in 34% to 53% yield. (Scheme 42)[100]

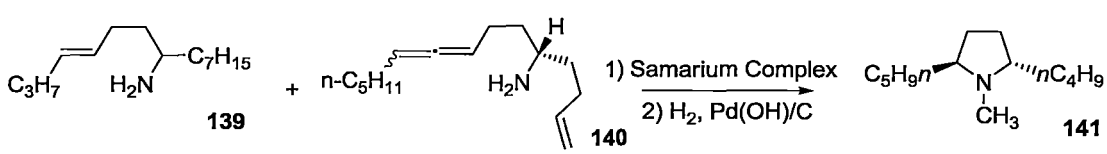


Scheme 42 – Synthesis of *cis*-5-substituted proline derivatives

While these are effective approaches for the syntheses of *cis*-5 or *cis*-3 substituted prolines, there is not a general approach towards these derivatives.

Other Pyrrolidines

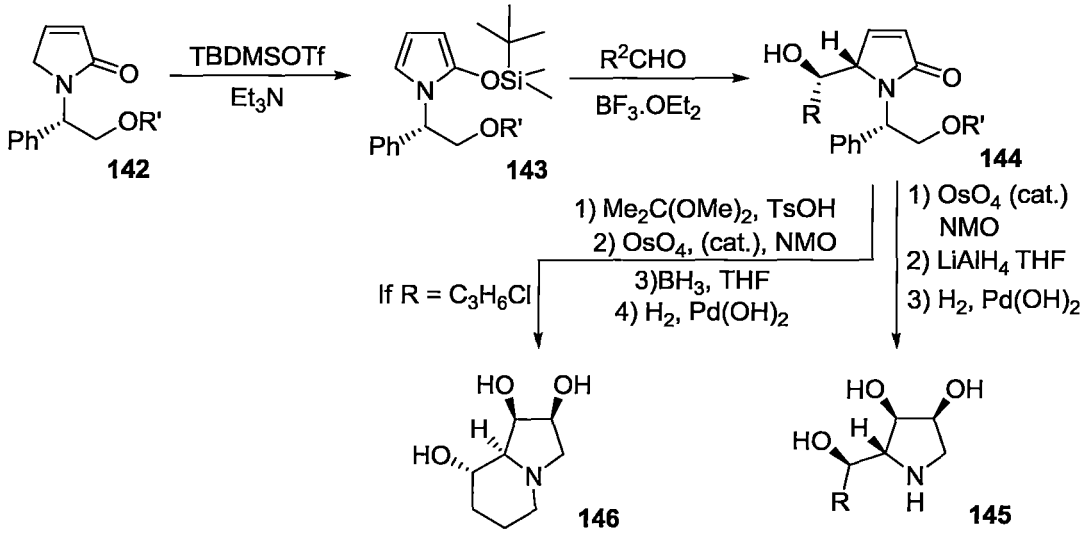
While the substituted proline derivatives often difficult to synthesise, they only require a variation of one group, as a carboxylic acid is at C2. Other pyrrolidine derivatives can therefore be considered highly complex, as up to five substituents may be present on the ring, making syntheses potentially very difficult. Take for example the relatively simple alkaloid pyrrolidine 197B (**141**), which is an ant venom.[101] Marks and co-workers proposed the synthesis using an organosamarium complex as a catalyst to cyclise the amino alkenes **139** and **140** to give the *trans*-pyrrolidine **141**. (Scheme 43) Although this reaction gave a good yield of the backbone, this was not straightforward and as the substituents were introduced at an early stage, it is not trivial to adopt multiple targets.



Scheme 43 – Formation of pyrrolidine 197B *via* cyclisation of amine

Royer and co-workers also illustrated an example of the synthesis of polyhydroxylated pyrrolidines **145** or an aza-sugars **146** as they are referred to. Lactam **142** was converted to 2-silyoxypyrrole **143** and underwent a Lewis acid promoted aldol reaction to introduce the substituent onto the ring. This intermediate **144** contains an alkene which was used as a handle to introduce a diol stereoselectively. Reduction results in the removal of the chiral auxillary. It gave the tri-substituted pyrrolidine derivative **145**. They also demonstrated that suitably

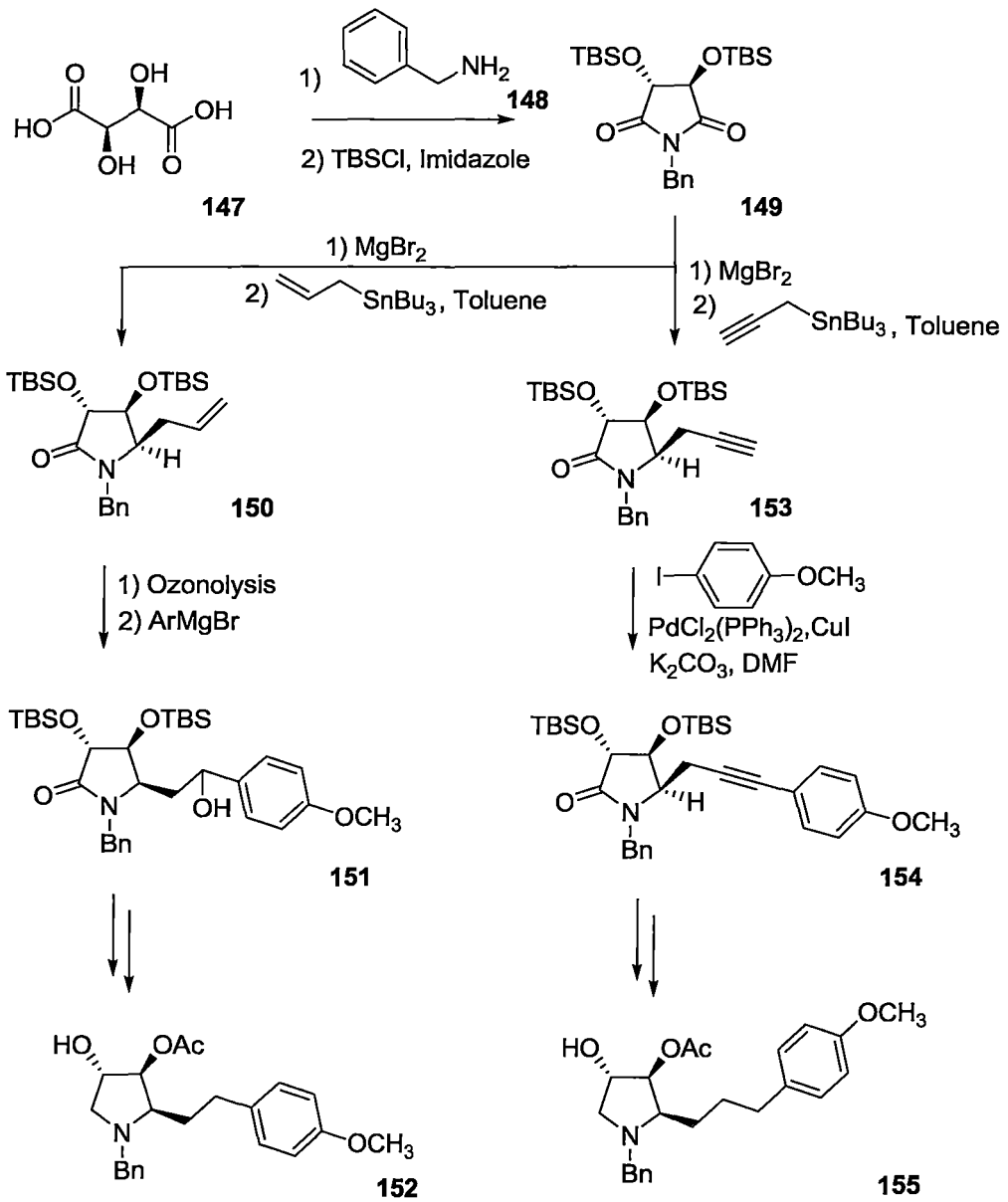
substituted side-chains of the indolizidines, such as derivatives of swainsonine **146** could be obtained.[102] (Scheme 44) Compounds of this type are highly sought after as swainsonine has interesting biological effects, such as anti-cancer, anti-tumor and immunoregulating activities.[103] This highlights the importance of a synthetic procedure that can be used to access multiple targets from a readily formed intermediate.[104]



Scheme 44 – Formation of polyhydroxylated pyrrolidines

In conjunction with the syntheses of natural products, it is also of great interest to synthesise synthetic analogues for evaluation of SAR, and to discover new lead compounds. As for pyrrolidine derivatives, the main modifications are to vary the stereochemistry or omit substituents. Another approach is to include extra carbon atoms between key functional groups within a molecule. Kim *et al.* also reported the synthesis of anisomycin derivatives with extended side-chains, possessing two and three carbon atoms between the aromatic ring and the pyrrolidine.[105,106] Tartarimide **149,** derived from tartaric acid, is a common intermediate for the formation of the two and three carbon spacer pyrrolidine derivatives. (Scheme 45)

The side-chains were introduced by amidoalkylations with ethyl and propargyl stannanes.[99] The two-carbon spaced pyrrolidines were formed *via* ozonolysis of the alkyl derivative, reacted with a Grignard reagent, a series of elimination reduction and deprotection, to give **152** in 34%. The three-carbon spaced derivative **155** was obtained from the propargyl intermediate **154** by the Sonogashira palladium cross-coupling reaction to introduce the aryl group onto the three-carbon spaced side-chain. The synthesis was completed by a series of reductions; deprotection and selective acetylation. However to date, the activity of these modifications has not been reported. Although this synthetic pathway gave stereo control, the method involved uses stannanes which is not ideal as tin contamination is not desirable.



Scheme 45 – Syntheses of anisomycin derivatives

Aim

Many synthetic approaches have been exploited by research groups; for the synthesis of pyrrolidines with cyclisation to form the heterocycle, being a common key step for the formation of pyrrolidines. Often the synthetic method is not flexible for the synthesis of multiple targets from a common or advanced intermediate, as the substrates are introduced at an early stage.

As described in chapter 1, pyrrole is a nitrogen-containing five membered electro rich ring system that can be substituted at all five positions. Therefore it was considered that pyrrole could be exploited for the formation of pyrrolidines. Hence, the combination of regioselective substitution of pyrrole and the elaboration to pyrrolidines or proline derivatives depends upon the substrates. There is even potential to control the dearomatisation of pyrrole *via* either catalytic hydrogenation or partial reduction.

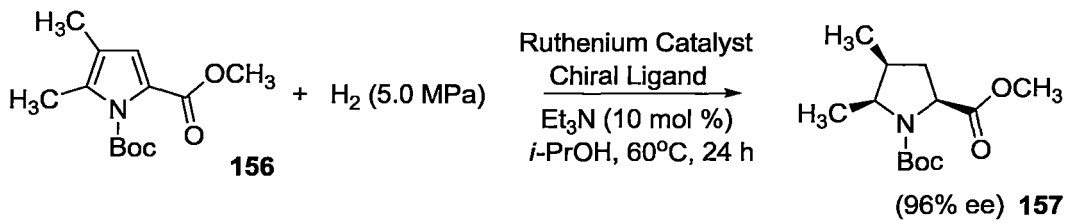
By employing the partial reduction of pyrroles, a synthetic pathway would be developed for the generating of pyrroline intermediates which can be elaborated further. Examples of these natural products are anisomycin (**99**), codonoposinine (**100**) and preussin (**101**). These natural products all contain hydroxyl groups at C3 and C4 and while this would be difficult to introduce at the pyrrole stage, it could be done readily at the pyrrolidine oxidation state.

Review of Reduction of Pyrroles

Catalytic Hydrogenation

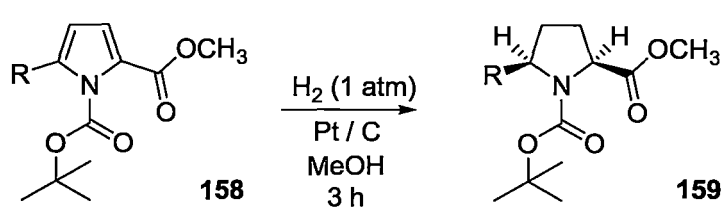
The reduction of electron-rich pyrroles is difficult due to the high electron density of the heterocyclic ring and in the previous chapter we exploited this property to successfully reduce chlorides attached to the pyrrole ring. For pyrroles to be reduced readily, the electron density of the system should be reduced. Recently Kuwano *et al.* reported an asymmetric catalytic hydrogenation of a substituted

pyrrole for the formation of a chiral proline skeleton with *cis* relationship of the 3 substrates **157**.[107] (Scheme 46) The reaction proceeded readily on *N*-Boc pyrrole **156**, derived with a ruthenium catalyst and a chiral ligand. The saturated system was formed in good yield with high ee but a high pressure of hydrogen was required.



Scheme 46 – Catalytic asymmetric hydrogenation

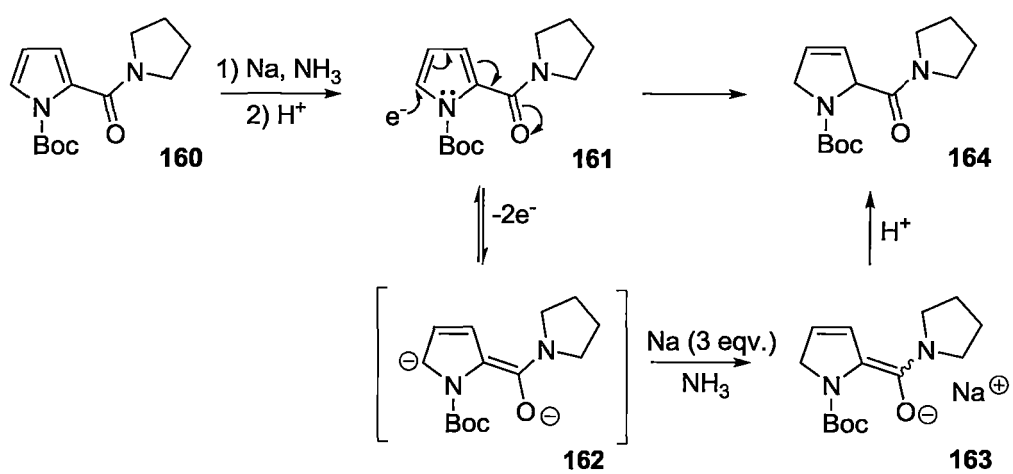
For a much milder reduction method Muchowski *et al.* reported that catalytic hydrogenation of methyl-5-substituted pyrrole-2-carboxylate, such as **158** with platinum on carbon at 1 atmosphere of hydrogen, gives only one stereoisomer of the *cis*-pyrrolidine derivatives **159** in good yield.[70] As for the previous example, only the *cis* isomer is observed and indicates that catalytic hydrogentation of poly-substituted pyrroles is stereospecific. (Scheme 47)



Scheme 47 – Muchowski's Catalytic hydrogenation

Partial Reduction of Pyrroles – Birch reduction

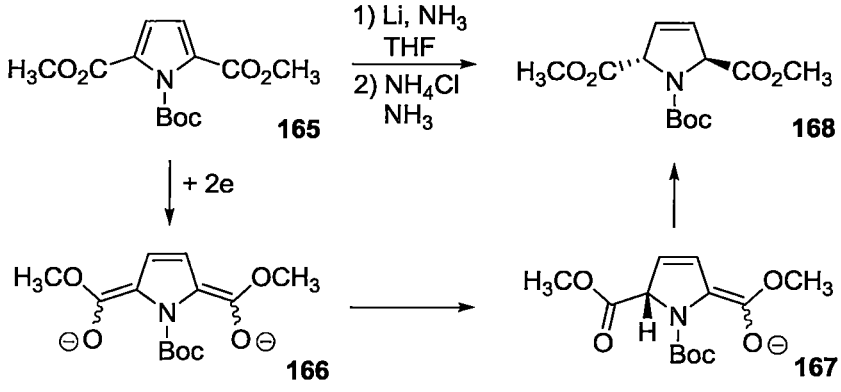
The partial reduction of pyrrole is not common, and only a small number of examples have been reported. Typically pyrroles do not undergo Birch reduction due to the high electron density hindering the addition of an electron. However the key, like catalytic hydrogenation, is the activation of electron withdrawing groups. An ester or amide at C2 and a butoxycarbonyl at the nitrogen is an example.[2,108] Donohoe and co-workers established a series of modified Birch reductions on electron deficient pyrroles to give pyrrolidine derivatives. It was demonstrated that using group I and II metals in ammonia can reduce pyrroles to give pyrrolines **164** in good yields.[108] (Scheme 48) Donohoe proposed that the reduction take place to form dianion **162**, followed by protonation from ammonia to give enolate **163**. Protonation then forms pyrroline **164**.[2,108,109] Alkylation of the enolate has also been demonstrated.



Scheme 48 – Birch Reduction using Group I and II metal in ammonia

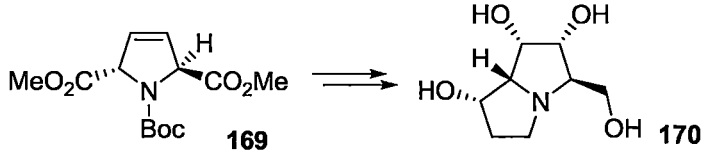
Donohoe reported that the best substrates contain esters at C2 and C5 and a Boc group on nitrogen, such as **165**, could form the stable dianion **166**. Protonation or

alkylation of the enolate **167** occurs yielding the pyrroline product **168** with *trans* isomer selectively at C2 and C5 in high yield.[109] (Scheme 49)



Scheme 49 – Donohoe's modified Birch reduction

The pyrroline product contains an alkene and this can then be exploited for synthesis. Donohoe applied this partial pyrrole reduction towards the syntheses of the naturally occurring polyhydroxylated pyrrolizidines, such as 1-epiaustraline **170** and other australine derivatives by dihydroxylation of the pyrroline intermediate **169**.[109-111] (Scheme 50)

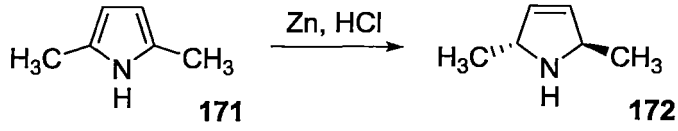


Scheme 50 – Synthesis of 1-epiaustraline

Knorr-Rabe Partial Reduction of Pyrrole

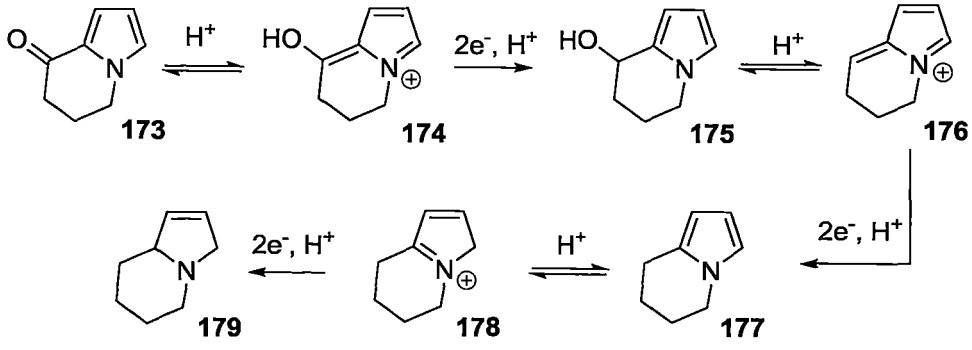
Donohoe's partial reduction however does not work with more electron rich pyrroles and therefore it cannot be used for more typical electron rich pyrroles. In 1901 Knorr and Rabe reported that electron rich alkyl pyrroles **171** reacted with

powdered zinc and hydrochloric acid (5 M) to give 3-pyrroline **172.**[112] (Scheme 51) This reaction has only been used a few times since it was first reported over 100 years ago.[113-115] Perhaps yields were not high and reaction conditions were relatively harsh.



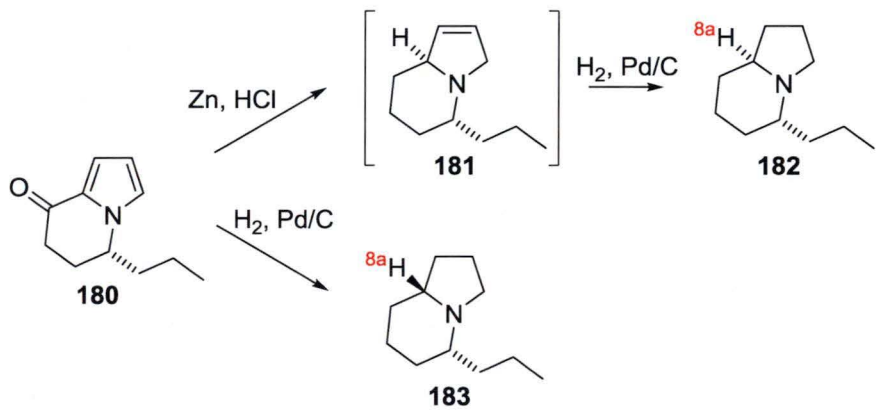
Scheme 51 – Knorr's and Rabe's Partial Reduction

Recently Smith *et al.* reported that when α-ketopyrrole **173** reacted with zinc metal and concentrated hydrochloric acid in hot methanol over 10 minutes, the corresponding pyrrolidine **179** was obtained in high yield.[73] (Scheme 52) This skeleton partial reduction of pyrrole is the first example that contains one carbonyl group, but it should be noted that the carbonyl is also reduced in the final product. The mechanism proposed by Smith was a protonation of the carbonyl group to give a conjugated iminium ion **174**. Therefore this exploited the electron density of the heterocycle. A series of reduction and protonation processes gave pyrroline **179**. The lack of fully saturated pyrroline was one apparent difference in the method of Knorr and Rabe.



Scheme 52 – Smith's proposed mechanism for α-ketopyrrole reduction

Although these harsh conditions are not compatible with many functional groups such as esters, Smith has exploited this methodology for the formation of pyrrolidine **182** which was hydrogenised in the synthesis of the epimer of the frog toxin, indolizidine 167B.[73] (Scheme 53) This stereochemical outcome is in contrast to that of catalytic hydrogenation.[73] This is an example of the choice of addition, resulting in the opposite stereochemical outcome at C8a while hydrogenation delivers hydrogen to the least hindered face. The Zn / HCl reduction by contrast is from the most hindered face. It has been hypothesised that this may be due to the addition of zinc on the least hindered face.

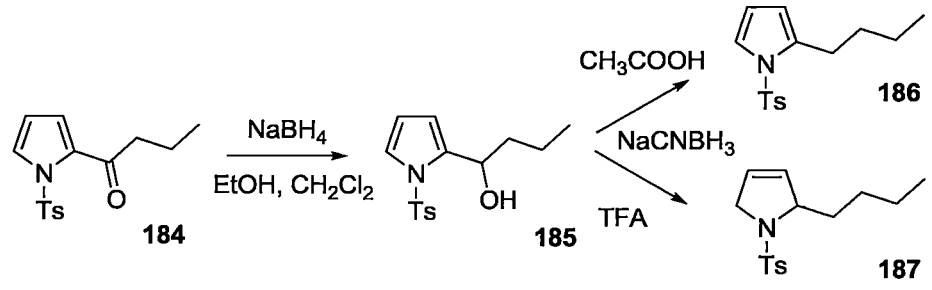


Scheme 53 – Synthesis of indolizidine analogue

Partial Reduction via Metal hydride – Acid

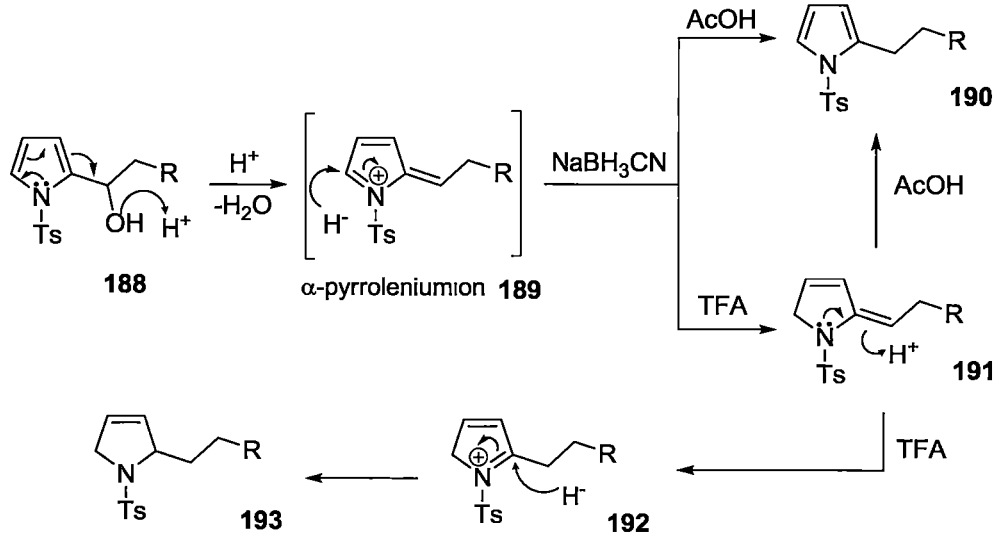
A mild alternative for the reduction of α-keto pyrroles has been reported by Ketcha who demonstrated that *N*-tosylpyrrole derivatives can be reduced to the corresponding pyrrolines by reaction with $NaBH_3CN$ in TFA.[116] Work within the group has extended this chemistry and showed that *N*-tosylpyrrole **184** was first reduced to the stable α-hydroxy pyrroles **185**. Further chemoselective reduction can be achieved using trifluoroacetic acid. The corresponding pyrrolines **187** are

obtained if TFA is used as the solvent, and the alkyl pyrrole **186** obtained when acetic acid is employed.[117] (Scheme 54) Due to the mild conditions used, this is complementary to the harsh conditions reported for the zinc / HCl method.[73]



Scheme 54 – You's partial reduction *via* metal hydride/acid

The mechanism proposed is similar to that of zinc reduction. (Scheme 55) The α-hydroxy pyrrole dehydrates under acid conditions giving the α-pyrroleniumion **189** which is reduced to enamine **191**. It is proposed that with the presence of a strong acid source, such as TFA, the enamine **191** can be protonated to iminium **192** followed by reduction yielding pyrroline **193**. On the other hand, without a sufficient acid source, **191** can simply tautomerise to the alkyl pyrrole **190**.[117]

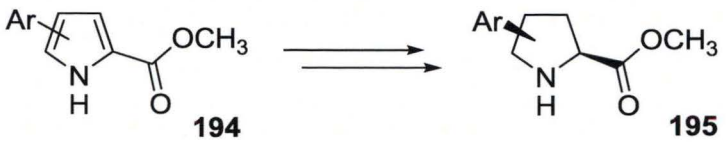


Scheme 55 – You's proposed mechanism

Therefore from the literature precedent, there are two clear methods that can be exploited for the transformation of pyrroles to pyrrolines. They are catalytic hydrogenation and partial reduction. However, partial reduction offers an advantage as the formation of the alkenes of the 3-pyrrolines can be functionalised further. Therefore derivatives of this type could be used as potential building blocks in synthetic chemistry.

Discussion Outline

While individual compounds can be synthesised by one of numerous synthetic methods, the importance of building blocks and their use in the pharmaceutical industry for the synthesis of novel compounds has greater potential than their application to natural products synthesis. Correspondingly, it was considered that these reduction methodologies could be exploited for the formation of 3-pyrrolidines as molecular scaffolds or templates. The advantage is utilising the reactivity of pyrrole to control the placement of substituents onto the five-membered ring before the formation of the 3-pyrrolines or pyrrolidines, depending upon the reduction method. The arylpyrrole-2-carboxylates formed in part 1 will be employed in this reduction chemistry to extend the synthesis of the compounds towards the preparation of simple proline analogues. The C3, C4 and C5 mono-aryl pyrrole-2-carboxylates **194**, will be used to synthesise the *cis*-C2,3, *cis*-2,4 and *cis*-2,5-disubstituted prolines **195**. (Scheme 56)



Scheme 56 – Synthesis of aryl-substituted prolines

The chemistry developed by the Smith group will be adapted to use α-ketopyrroles as a template by exploiting the partial reduction conditions as described above for the formation of 3-pyrrolines. These pyrrolines will be further functionalised to target analogues of natural products such as anisomycin, preussin and codonoposinine.

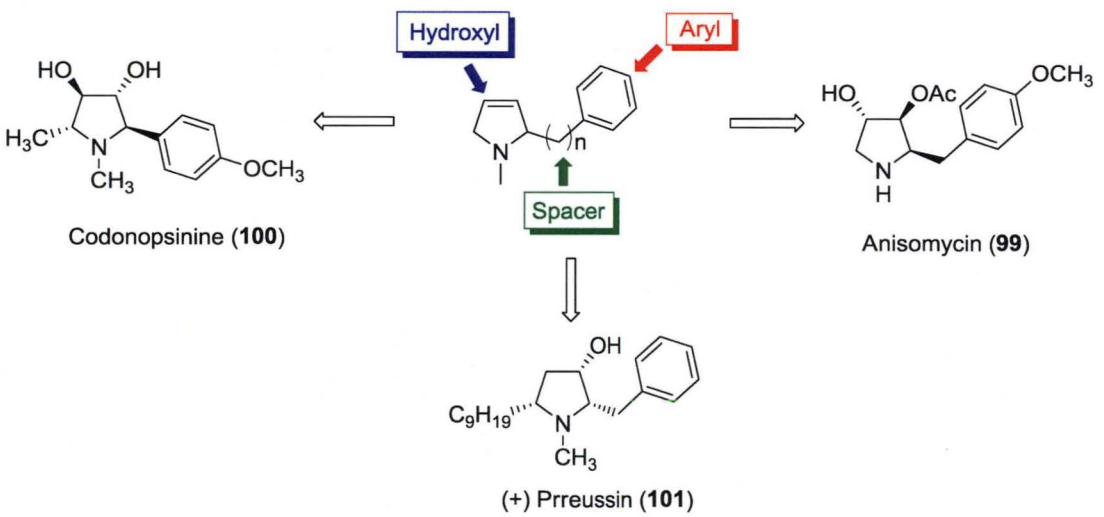
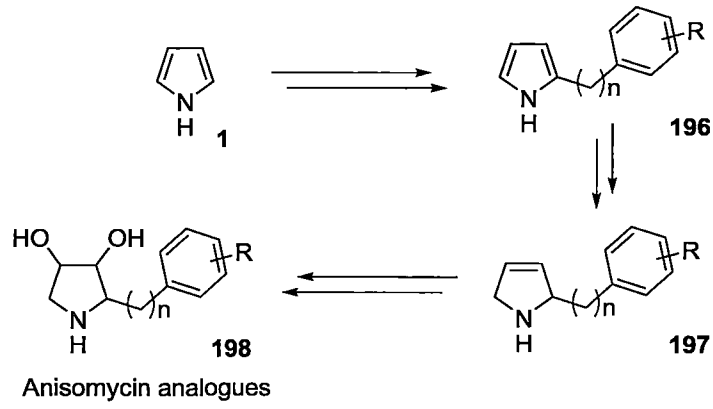


Figure 10 – Key features of pyrrolidines



Scheme 57 – Proposed Synthetic Scheme

The common features of these pyrrolidines are that they contain one or two hydroxyl groups at C3 and C4. They also have an aryl group joined to C2 of the pyrrolidine ring with or without a one carbon linker. (Figure 10) The partial reduction of a pyrrole will give a pyrroline that can be used to introduce one or two hydroxyl groups by dihydroxylation or hydroboration. The objective for this part of the project is to construct the core structure **196**, utilising standard chemistry of the reactive pyrrole core, followed by rapid partial reduction to give 3-pyrroline **197**. The pyrroline will then be dihydroxylated to yield substituted pyrrolidines **198**. (Scheme 57) These compounds would be structural analogues of anisomycin. These pyrrolidines are one of the most common motifs found in pyrrolidine natural analogues; hence, the aim is to develop the methodology for the rapid construction of a non-natural compound library.

Chapter 3

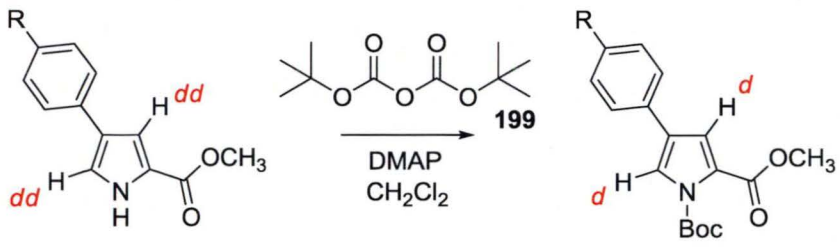
Formation of Proline Analogues

3.1 Formation of cis-4-Aryl-Proline Analogues

As demonstrated in chapter 1, the heterocyclic ring of arylpyrrole-2-carboxylates is not reduced under standard hydrogenation conditions with palladium on carbon, due to the electron rich system. Therefore an electron withdrawing group is required to activate the pyrrole for reduction to occur. Muchowski demonstrated that an electron drawing group such as Boc, on the nitrogen can reduce electron density.[70] *tert*-Butoxycarbonyl (Boc) is one of the most commonly used protecting groups in organic chemistry due to its stability under common reactions, and the ability to be removed easily under mild acidic conditions.[84,118,70,119] In this mixture, the Boc group does not play a protecting group role, but is involved directly for activation. Therefore, to activate the aryl-pyrroles, they must first be reacted with Boc anhydride (Boc_2O), with catalytic amounts of 4-dimethylaminopyridine (DMAP) in dichloromethane.[84]

Reaction of 4-arylpyrrole-2-carboxylates (**60** - **62**) with Boc_2O in dichloromethane with catalytic amounts of DMAP gave the corresponding *N*-Boc pyrroles (**200** – **202**) in good to high yields. (Scheme 58) The compounds were characterised by the loss of the N-*H* at ~10 ppm in the ^{1}H NMR spectrum, as well as a change in the splitting pattern of the pyrrolic protons at C3 and C5, which resonate as doublets at 7.08 and 7.49 ppm (J = 2.0 Hz), since the coupling to the N-*H* was removed. Examination of the ^{1}H NMR spectrum also indicated the introduction of the Boc group with a singlet resonating at ~1.5 ppm with an integration ratio of 9. Examination of the ^{13}C NMR spectrum also confirms the addition of Boc by showing a new resonance at 28 ppm.

Mass spectroscopy gave the correct molecular ions to confirm the formation of the activated *N*-Boc pyrroles.

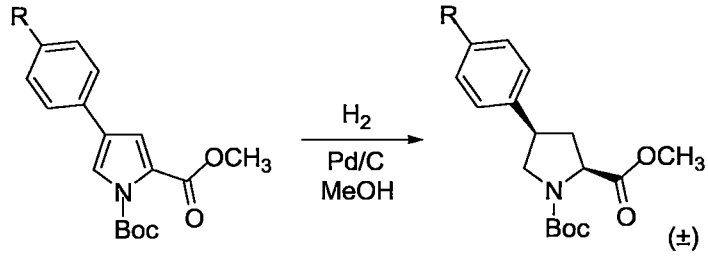


	R	% Yield
200	H	65%
201	$-CH_3$	Quant.
202	$-OCH_3$	Quant.

Scheme 58 – *N*-Activation

The activated pyrroles were subjected to catalytic hydrogenation with palladium on carbon in methanol at 40 psi in a Parr shaker hydrogenated for 6 h, during which time the starting material was consumed. (Scheme 59) The solvent was removed, the products purified and analysed using NMR spectroscopy. In the case of the 4-phenyl derivative **203**, the reduction of the pyrrole ring was indicated by the loss of the doublets at 7.13 and 7.58 ppm and the presence of multiplets at 2.10, 2.65, 3.37, 4.20 and 4.38 ppm for the pyrrolidine protons. Examination of the ^{13}C NMR spectrum also showed the aliphatic carbons at 28.51, 38.38, 43.20, and 59.82 ppm. Full characterisation of the ^{1}H NMR is not easy, since the compounds showed a ~5:1 mixture of rotomers. In comparison, it is consistent with literature values reported by Doherty for this compound.[120] In contrast to the *N*-Boc-*trans*-proline methyl

ester, the ^{1}H NMR spectrum indicates two distinctive resonances at 4.00 and 4.55 ppm. Therefore the formation of the *cis* isomer was confirmed.[121]



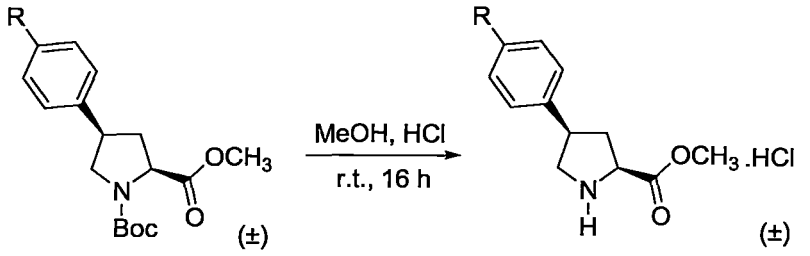
	R	% Yield
(±) **203**	H	68%
(±) **204**	$-CH_3$	61%
(±) **205**	$-OCH_3$	74%

Scheme 59 – Catalytic Hydrogenation

The ^{1}H and ^{13}C NMR spectra of **204** and **205** also showed these same features, except for the methyl group for the tolyl group of **204** at 2.31 ppm and the methoxy group of **205** at 3.77 ppm. As the ^{1}H NMR spectrum indicated, the compounds existed as a mixture of rotomers. Deprotection was carried out to simplify the spectra and characterised the *cis*-proline methyl esters.

Typically Boc protecting groups can be easily removed under relatively mild acidic conditions, such as trifluoroacetic acid in dichloromethane.[70] However, only decomposition was observed under these conditions with this system. As an alternate method, the *N*-Boc protected prolines were reacted with methanolic HCl and were formed by the careful addition of thionyl chloride ($SOCl_2$) to methanol.

After 16 h at room temperature, the solvent was removed to yield the corresponding HCl salt of the proline methyl esters in good yields. (Scheme 60)



	R	% Yield
(±) **206**	H	98%
(±) **207**	-OCH_3	64%

Scheme 60 – Deprotection

Examination of the ^1H NMR spectrum showed an obvious loss of singlet at ~1.43 ppm indicating the loss of the Boc group, while mass spectrometry also indicated the correct $[M-H]^+$ ion confirming the product formation. In the case of 4-methoxyphenyl proline methyl ester **207**, full assignments of the pyrrolidine protons were determined by the 2D-COSY and HSQC experiments. (Figure 11) The methine at C2 appears as a doublet of doublets at 4.67 ppm (J = 10.4 and 7.6 Hz). The methylene at C5 is indicated as a multiplet at 3.88 and a triplet at 3.36 ppm (J = 11.07 Hz). The methine at C4 resonates as a multiplet at 3.61 ppm and is observed by the two methoxy groups as well as one of the protons on C5. Finally the methylene at C3 appears as a doublet of triplets at 2.24 ppm (J = 13.1 and 10.9 Hz) and a multiplet at 2.83 ppm.

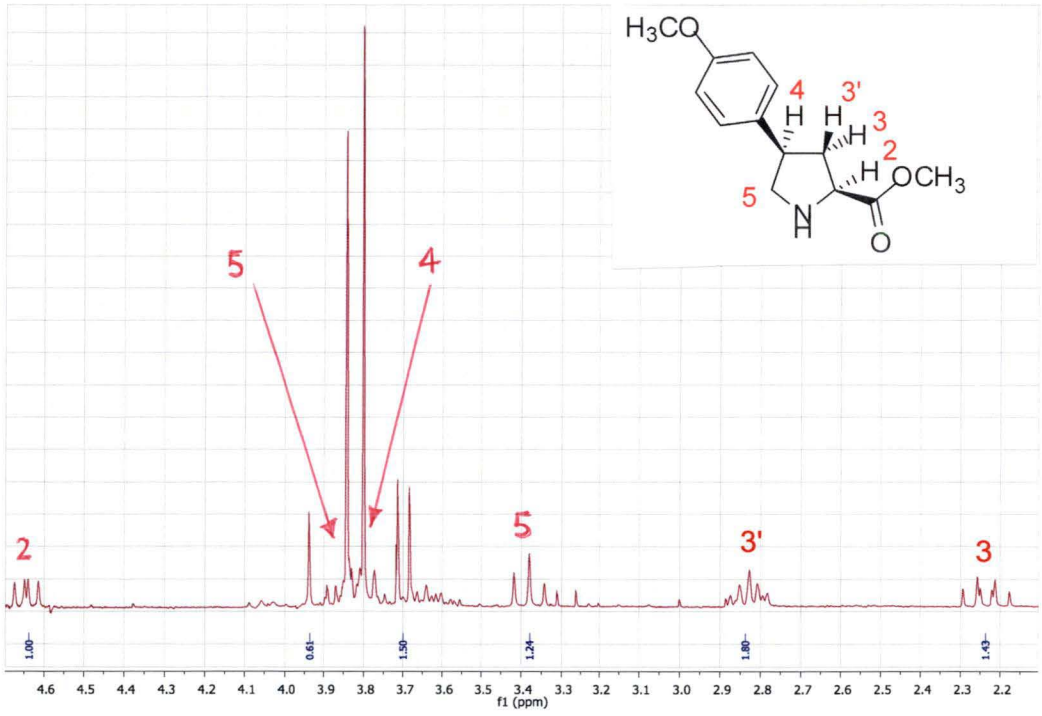
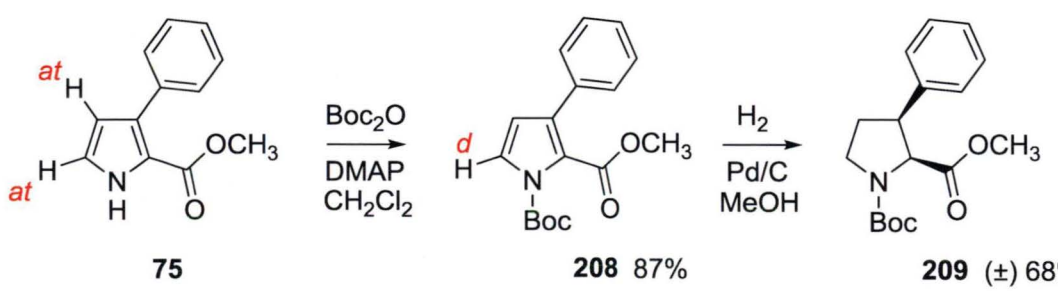


Figure 11 - ^{1}H NMR spectrum for *cis*-4-*p*-methoxy phenyl proline methyl ester **207**

The ^{1}H NMR spectra of the corresponding phenyl derivatives has not been reported,[122-124] and there is no *trans* isomer reported. However, it has for the *tert*-butyl ester and is in good agreement.[125] The NMR data is also consistent with the *cis*-4-phenyl proline HCl salt as reported by Hruby.[97] The findings were also in contrast to the *trans*-4-phenyl proline.[96] The reported pyrrolidine protons are resonated at 2.49, 2.73, 3.39, 3.57, 3.97 and 4.68 ppm. Hence, this is a good indication that the desired *cis* products were formed.

3.2 Formation of cis-3-Aryl Proline Analogues

Due to the success in the formation of *cis*-4-aryl proline methyl esters, this method was applied to the synthesis of the *cis*-3-aryl prolines which are considered constrained phenyl alanine derivatives.[99] Again, the Boc is required for activation of the electron rich pyrrole. Hence, methyl 3-phenylpyrrole-2-carboxylate (**75**) was reacted with Boc_2O in the presence of DMAP to give the activated pyrrole **208** in excellent yield. (Scheme 61) The product was confirmed by NMR spectroscopy, which was indicated by the loss of board *N*-H peak at 8.02 ppm, and the presence of a singlet at 1.58 ppm in ^{1}H NMR spectrum. One of the pyrrolic protons appears as a doublet at 6.33 ppm due to the loss of coupling with the N-*H*, while the second pyrrolic protons was overlapped with the aromatic signals. ^{13}C NMR and mass spectroscopy also supported the formation of **208**.



75 **208** 87% **209** (±) 68%

Scheme 61 – Formation of 5-phenyl-*cis*-proline

To obtain *cis*-3-aryl proline methyl ester **209** the activated pyrrole **208** was hydrogenated with palladium on carbon under the same conditions as for the reductive dechlorination as described in chapter 1. The formation of the *cis*-3-phenyl *N*-Boc proline methyl ester **209** was confirmed by ^{1}H NMR, showing the loss of the pyrrolic proton at 6.33 ppm. The appearance of pyrrolidine protons for

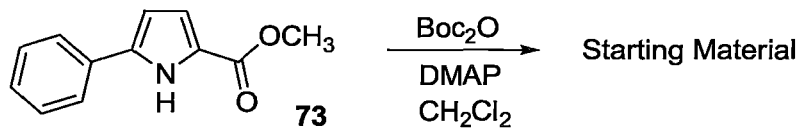
C3, 4 and 5 are resonated in the aliphatic region as multiplets at 2.13, 2.62, 3.47, 3.70 and 3.91 ppm. The compound is present as a mixture of rotomers as there are two doublets at 4.46 and 4.55 ppm for the C2 methine in a ratio of 4:6. The ^{13}C NMR spectrum also indicated rotomers due to the doublets of some of the aliphatic carbon signals. The spectral data was also consistent to that reported in literature.[100] The findings were also compared to the reported *trans*-3-phenyl proline methyl ester,[126,127] which showed two doublets at 4.24 and 4.38 ppm for the methine proton at C2, therefore indicating that epimerised has not occurred under the conditions.

Due to insufficient material, however, no further investigation was carried out. Nevertheless, a synthetic pathway for the constrained phenylalanine derivatives was successfully implemented as only deprotection is required, which was formed previously. The key to this synthesis was the regioselective modification of pyrroles, coupled with the reduction of electron deficient pyrroles *via* catalytic hydrogenation. It should be noted that the hydrogenation conditions used for heterocycle reduction were the same as for dechlorination, therefore indicating the chemoselectivity that can be achieved by controlling the electron density of the pyrrole system.

3.3 Formation of cis-5-Aryl-Proline Analogues

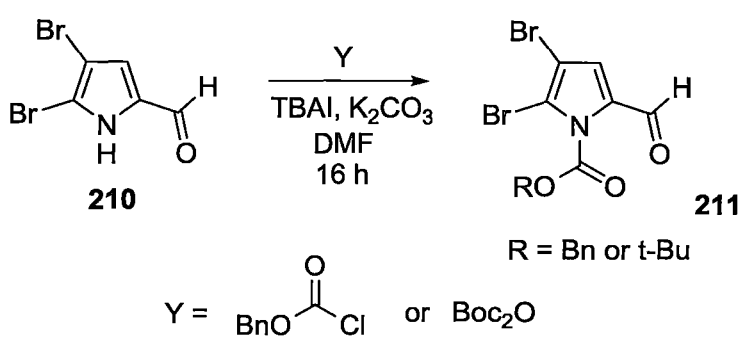
The above synthesis successfully demonstrated the formation of C4 and C3-aryl-proline analogues. To complete the general synthesis, C5-arylated pyrroles were

also investigated. However, in the case of the 5-phenyl pyrroles **73**, the activation with Boc_2O proved to be problematic. Under the standard *N*-Boc conditions, ^1H NMR spectrum indicated that only starting material was retrieved. (Scheme 62)



Scheme 62 – Activation

At first, steric effects were considered to be the problem. Recently, Handy demonstrated the installation of protecting groups with benzyl chloroformate or Boc_2O on hindered and electron deficient pyrroles using tetrabutylammonium iodide (TBAI) as a catalyst.[128] (Scheme 63) TBAI was used to generate iodoformate in situ which is more reactive and forms the corresponding carbamate **211**. This was shown to be effective for the synthesis of 5-bromo-pyrrole-2-carboxylate aldehydes; yields can be varied from 33 – 78%. Due to this success, we attempted this method for activation.

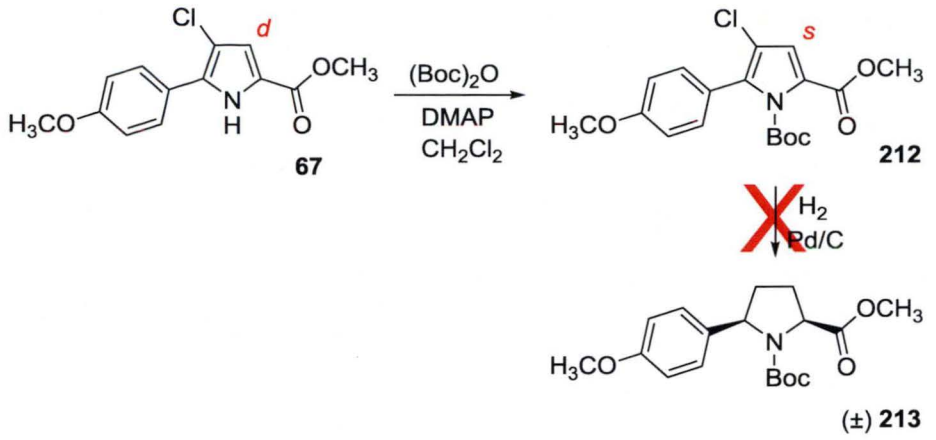


Scheme 63 – *N*-Protection with TBAI

As a result, 5-phenyl pyrrole **73** was reacted with Boc_2O with the presence of TBAI (1 equiv.) in DMF and potassium carbonate as a base. ^1H NMR analysis of the crude

mixture however only showed the starting material. Despite several attempts to modify the conditions, such as increased stoichiometry, reaction times and temperature, only starting material was recovered.

However, due to insufficient material of **73**, a different substrate and approach were employed for further investigation. The activation was attempted on the *p*-methoxyphenyl chloride substrate **67**. In theory, the electron withdrawing group, such as Boc, could reduce electron density from the pyrrole and promote the reductive dechlorination as well as the reduction of pyrrole to the corresponding proline derivatives in one pot, saving one synthetic step. Therefore, pyrrole **67** was reacted with Boc_2O in the presence of DMAP. (Scheme 64) Examination of ^1H NMR spectrum of the crude mixture suggested the formation of the desired product. The only pyrrolic proton at C3 resonated as a singlet at 6.88 ppm in ^1H NMR spectrum as expected, due to the loss of the coupling with N-*H*, and a new resonance at 1.37 ppm indicating the presences of the Boc group. Mass spectroscopy supported the product formation with molecular ions of 365 and 367 with a ratio of 3:1. The reason for this reaction occurring on this substrate, compared to the 5-phenyl derivative **73** is not clear. While the *p*-methoxyphenyl substituted at C5 may increase the nucleophilicity of the pyrrole, it would not normally be expected to have such a large effect.



Scheme 64 – *N*-Boc Activation for C5-aryl pyrroles

Nonetheless the activated pyrrole was carried through to the catalytic hydrogenation under the standard conditions as previously described. Unfortunately, no reduced products in any form were observed by analysis of ^{1}H NMR spectrum or TLC. The cause of the failure in the catalytic hydrogenation is not immediately apparent, perhaps due to a mixture of electronic and steric effects. Due to insufficient material, an extensive study of catalysts and conditions was not conducted. One reason for this is that methods for synthesis of the C3 and C4 prolines are lacking most as C5 substituted proline could be readily derived from gyroglutamic acid methyl ester.[129,130] However, we have demonstrated the interesting chemistry for these substrates.

3.4 Conclusion

In conclusion, a synthetic method for the formation of C4 and C3 prolines has been successfully demonstrated by exploiting regio controlled substitution of pyrrole and

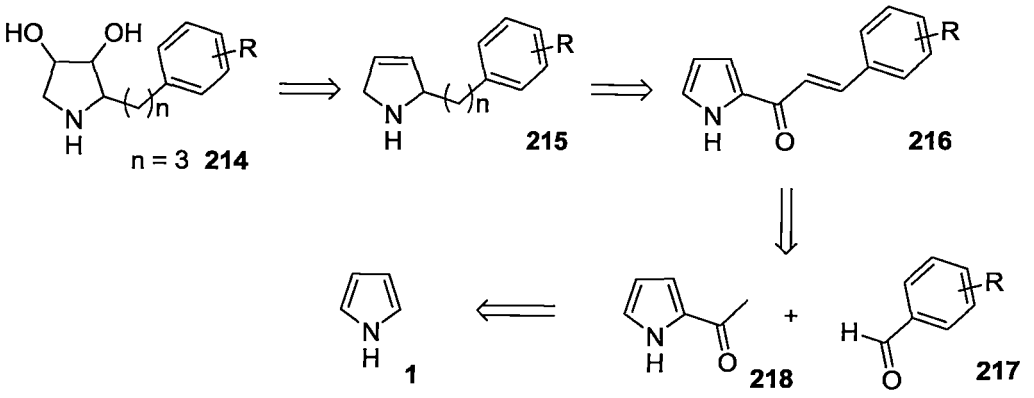
chemo and stereoselective hydrogenation of the heterocyclic ring. For future work, this methodology offers an attraction alternative for the rapid access to proline analogues, but to date has only demonstrated the preparation of the racemic products. The success of these mono-proline analogues could be extended and used as a chiral hydrogenation catalyst.[107] The poly-substituted proline analogues could also be formed by Sonogashira cross-coupling and potentially carried out the reduction, as reported.

Chapter 4

Three-Carbon Spaced Pyrrolidines Alkaloid Analogues

Chapter 4 – Three-Carbon Spaced Pyrrolidines

This chapter describes a short synthetic pathway for the synthesis of analogues related to the known biologically active pyrrolidine alkaloids. The key step will involve the partial reduction of pyrroles for the formation of a building block that can be used for further functional group manipulation. As mentioned previously, a pyrrolidine nucleus is at the core of many interesting and biologically active natural products. The substituents attached to this pyrrolidine core play a key role in the activity and binding of these compounds to an active site. The first compounds targeted will have a three-carbon spacer. This is due to the fact that the aryl function will be introduced on the pyrrole by a Claisen-Schmidt condensation of an aromatic aldehyde with 2-acetylpyrrole (**218**).[131] The advantage is that aromatic rings with varying degrees of oxygenation are present in many natural products, and the corresponding benzaldehydes are readily available. The substituted aryl derivatives targeted include 3,4-methylene-dioxy, 3,4-dimethoxy, and 4-methoxy, and will be used throughout this project. The 2-acetylpyrrole can be prepared by a Vilsmeier-Haack acetylation of pyrrole[132] but it is also commercially available. After the formation of aryl-α-ketopyrrole **216**, which sets the carbon skeleton of the analogues, partial reduction will form 3-pyrrolines **215**, which will then be used as a template to form dihydroxy substituted pyrrolidines **214**, another structural motif found in many natural products. (Scheme 65)

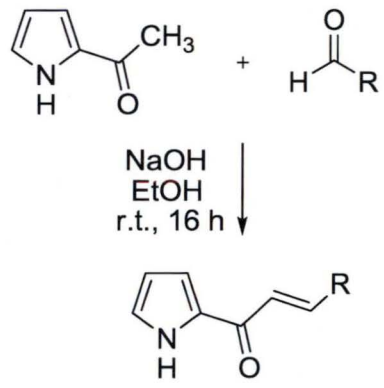


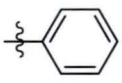
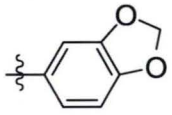
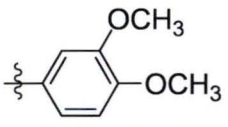
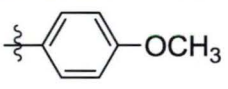
Scheme 65 – Retrosynthesis of three-carbon spaced pyrrolidines

4.1 Formation of α-ketopyrroles

The aldol condensation is one of the most operationally simple and reliable methods for the synthesis of α,β-unsaturated carbonyl compounds, particularly from an aromatic methyl ketone and an aromatic aldehyde. In this instance it is referred to as a Claisen-Schmidt condensation.[131,133] Therefore the Claisen-Schmidt condensation was chosen as the method for the connection of an aromatic aldehyde pyrrole using 2-acetylpyrrole (**218**) as the aromatic methyl ketone. As a result, 2-acetylpyrrole was treated with the corresponding benzaldehyde in alkaline ethanol at room temperature for 16 h. (Scheme 66) During this time the corresponding α,β-unsaturated ketones precipitated. All condensations occurred equally as well with the products being purified by recrystallisation and isolated in excellent yields. The formation of the products was confirmed using ^{1}H and ^{13}C NMR spectroscopy. In the example of the *p*-methoxy derivative **222**, the presence of the alkenyl protons were resonated as two sets of doublets at 7.25 and 7.80 ppm with a coupling constant of 15.6 Hz confirming the *trans* alkene formation. A single X-ray crystal structure was also obtained from the highly crystalline product **220** and

shows a high degree of planarity for the molecule indicating the extended conjugation of the two rings. (Figure 12)



	R	% Yield
219		95%
220		91%
221		85%
222		90%

Scheme 66 – Formation of α,β-unsaturated ketone *via* aldol condensation

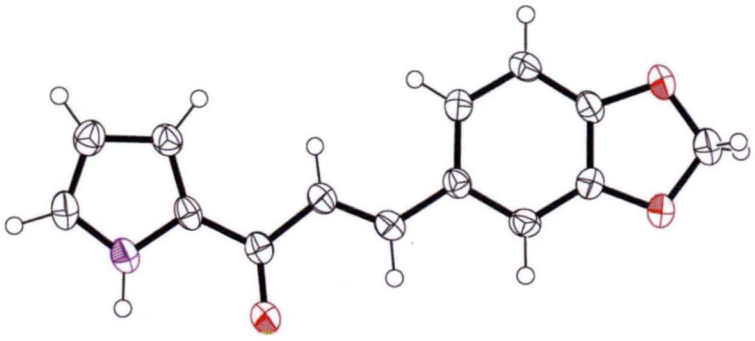


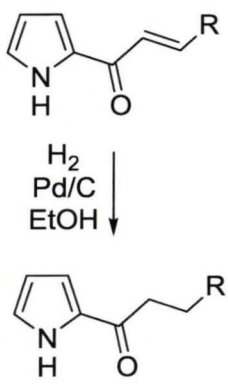
Figure 12 – An ORTEP diagram of compound **220** derived from X-ray crystallographic data (Purple = Nitrogen, Red = Oxygen)

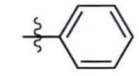
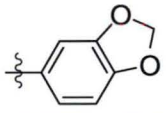
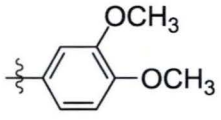
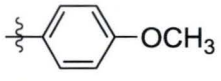
The carbon skeleton of the synthetic analogues of pyrrolidine natural products was therefore formed in this one simple step. Interestingly, the phenyl-α,β unsaturated ketone **219** has been reported previously as part of a library of chalcone derivatives, and itself has biological activity giving a positive result for anti-tumor activity against

human breast cancer cell lines. The report showed that pyrrolidine **219** was 5 to 10 fold more toxic to human breast cancer lines than normal breast epithelial cell lines with the IC_{50} ranging from 9 to 15 μM depending on the cell lines.[134,135]

The reduction of the pyrrole **219** to the pyrroline was first attempted under the conditions reported by Smith which involve the alternating addition of zinc dust and concentrated HCl to a hot solution of the compound in methanol.[73] Examination of the ^{1}H NMR spectrum of the crude mixture however only showed the starting material. The first step of reduction is believed to be the protonation of the carbonyl, forming an imminium ion, followed by reduction. As no reaction occurred, it was postulated that the conjugation of the carbonyl group to the aryl ring was the main factor in hindering this first step. This was suggested by the crystal structure of **220** indicating extended conjugation between the two rings by the almost planar shape of the compound. Therefore the alkene was removed by standard catalytic hydrogenation. As noted from previous experience, the heterocyclic ring system will not be reduced under standard catalytic hydrogenation conditions. α,β-Unsaturated ketones were therefore subjected to catalytic hydrogenation under standard conditions with palladium on carbon in ethanol. The α-ketopyrroles were obtained in excellent yields and characterised by ^{1}H NMR and ^{13}C NMR spectroscopy. (Scheme 67) Using the methylenedioxy derivative **224** as an example, the alkene protons were replaced with a new multiplet at 3.0 ppm integrated for four protons in ^{1}H NMR spectrum. The ^{13}C NMR spectrum also showed two signals at 40 and 30 ppm for the two new sp^3 hybridised carbons. More importantly, the pyrrole nucleus was still intact as indicated by the three

typical pyrrole resonances at 6.27, 6.90 and 7.03 ppm. The crystal structure of **224** was also obtained which showed that the structure is no longer planar, and therefore the partial reduction was expected to proceed. (Figure 13)



	R	% Yield
223		95%
224		95%
225		86%
226		80%

Scheme 67 – Partial reduction – Catalytic Hydrogenation

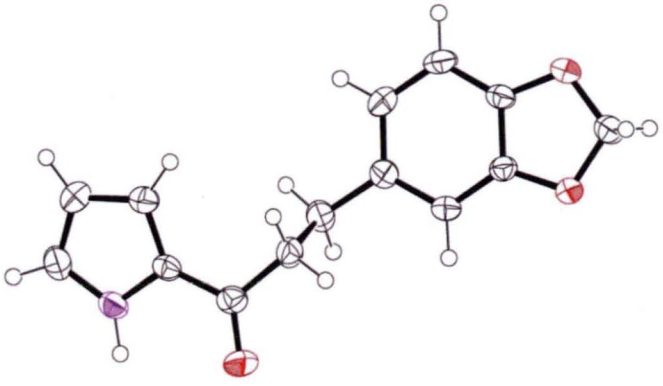
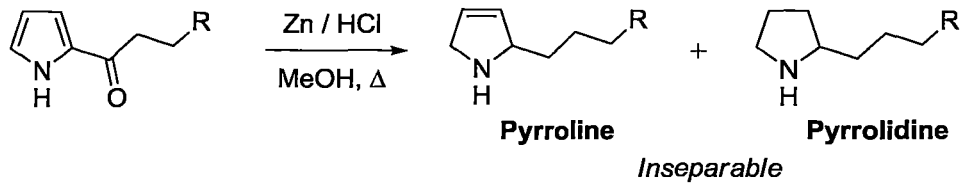


Figure 13 – An ORTEP diagram of compound **224** derived from X-ray crystallographic data (Purple = Nitrogen, Red = Oxygen)

4.2 Partial Reduction

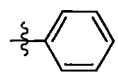
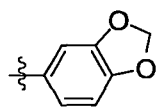
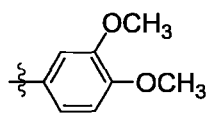
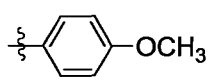
With the α-ketopyrroles in hand, they were subjected to the same Zn / HCl method as previously attempted. Therefore the reaction of pyrrole **224** by the addition of

small portions of powdered zinc (10 equivalents), followed by concentrated hydrochloric acid into a hot solution of methanol, rapidly consumed the starting material after 15 minutes. Quenching with ammonia to dissolve the zinc salts and extraction gave the crude products. (Scheme 68) On analysis of the ^{1}H NMR spectrum, the pyrrolic protons at 6.2, 6.9 and 7.0 ppm were no longer present, with multiplets appearing at 3.7, 4.0 and 5.7 ppm for the pyrroline protons. In particular, the two alkenyl protons at C3 and C4 at ~5.7 ppm are consistent with that of other pyrrolines reported.[115] The ^{13}C NMR spectrum indicated the key features, such as the loss of the carbonyl carbon at 189 ppm and the formation of the aliphatic carbons resonating at 28, 53 and 65 ppm, and are consistent with the formation of the product **229**. However, there was also a small amount of fully saturated pyrrolidine **230** observed, as the indicated additional resonances in the aliphatic region from 22 ppm to 60 ppm. Examination of the ^{1}H NMR spectrum also indicated this with the small resonance at ~2.5 ppm for the methine protons at C3 and C4 of the saturated pyrrolidine. This indicated an approximate ratio of 4:1 favouring the desire product. Purification was attempted *via* column chromatography. However the compounds were inseparable. Although this was seen as a problem, it was postulated that they could be separated after dihydroxylation.



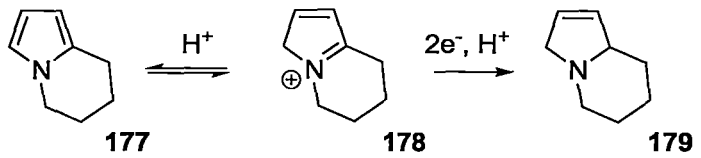
Pyrroline **Pyrrolidine**

Inseparable

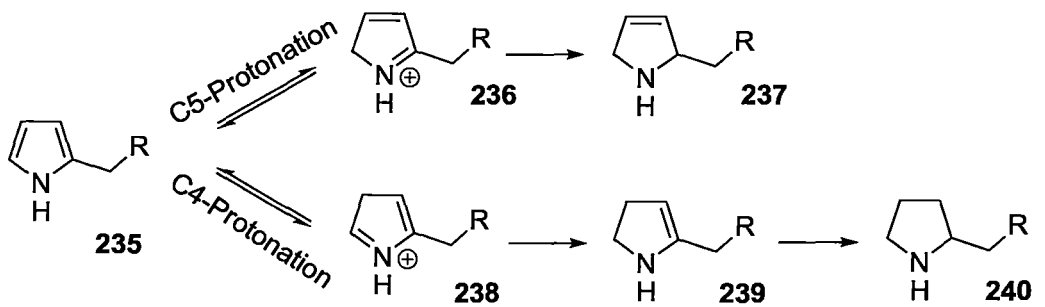
R	Pyrroline	Pyrrolidine	% Yield	Pyrroline vs Pyrrolidine
	**227**	**228**	Quantitative	5:1
	**229**	**230**	Quantitative	4:1
	**231**	**232**	Quantitative	5:1
	**233**	**234**	Quantitative	5:1

Scheme 68 – Partial Reduction of pyrrole *via* Zn / HCl

In the bicyclic ring system **177**, Smith reported that only 3-pyrroline **179** was obtained. (Scheme 69) He proposed that the intermediate bicyclic pyrrole **177** underwent selective protonation at C5. It is possible that the saturated pyrrolidine **240** assessed from competing protonation at C4 would yield an intermediate enamine **238** and would be reduced to 2-pyrroline **239**. (Scheme 70) This could be potentially reduced to the saturated system **240**. An alternative is that the alkene of the 3-pyrroline migrates under the acid conditions to give an enamine **236** that is reduced under the conditions.



Scheme 69 – Smith's bicyclic partial reduction



Scheme 70 - Partial reduction for pyrrolines and pyrrolidines

We predicted that the excess equivalents of zinc may contribute to the cause. Thus the amount of zinc was reduced from 10 to 8 equivalents in order to limit the over-reduction. In total, only 6 equivalents are required with the two reduction steps. However, the same ratio of 3-pyrroline to pyrrolidine was observed. Nevertheless, the reaction gave consistent and high yields of the key 3-pyrroline intermediates in three short steps.

4.3 N-Protection

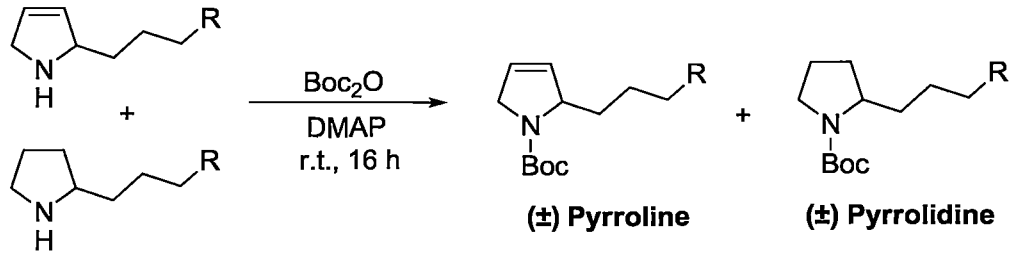
To obtain the dihydroxylated pyrrolidines, protection of *N*-H is required as free amines hinder dihydroxylation with osmium catalyst. Boc is one of the most common protecting groups for amine protection, therefore it was chosen.[119,136] The mixture of 3-pyrrolines **229** and pyrrolidines **230** was treated with one equivalent of

Boc_2O in the presence of DMAP under standard conditions as previously described. (Scheme 71) Surprisingly, *N*-Boc 3-pyrrolines and *N*-Boc pyrrolidines could be separated after purification by column chromatography on silica gel giving the unsaturated *N*-Boc pyrroline **243** in 79% yield, and the saturated *N*-Boc pyrrolidine **244** in 10% yield. For **243**, the presence of the Boc group was indicated by the singlet at 1.4 ppm in the ^1H NMR spectrum representing nine protons of the three methyl groups, while the methine at C2 also shifted from 4.0 ppm to 4.4 ppm due to deshielding from the Boc group. The unsaturated 3-pyrroline protons at C3 and 4 resonated at 5.6 ppm and confirmed the unsaturated product **243** formation. Examination of the ^{13}C NMR spectrum also indicated the product with only seven signals from 33 ppm to 85 ppm indicating the seven aliphatic carbons and two alkenes at 53.97 and 64.11 ppm. Mass spectroscopy also supported product formation with the correct molecular ion 331 supporting the formula $C_{19}H_{25}NO_4$.

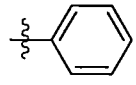
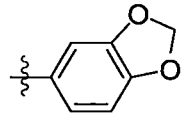
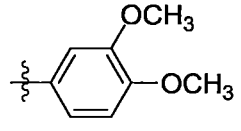
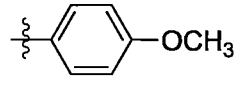
The saturated *N*-Boc pyrrolidine **244** was also identified by ^1H and ^{13}C NMR spectroscopy. The aliphatic protons resonated as multiplets from 1.5 to 3.2 ppm in the ^1H NMR spectrum with the methine proton at C2 resonating at 4.0 ppm. More importantly, examination of the ^{13}C NMR spectrum indicated nine signals in the aliphatic region from 25.5 ppm to 60.4 ppm representing the aliphatic carbons including the Boc group.

The other three derivatives also exhibited the same behaviour. The protected 3-pyrrolines were isolated in reasonable yield, and while 35% to 79% is not high, this is effectively the isolated yield over two steps. In summary, this short fast and

effective four step method allows the generation of the 3-pyrroline building blocks from commercially available starting materials, and methods that can be comfortably carried out on gram scale.



Inseparable *Separable*

R	Pyrroline (% Yield)	Pyrrolidine (% Yield)
	(±) 35% **241**	(±) 2% **242**
	(±) 79% **243**	(±) 10% **244**
	(±) 64% **245**	(±) 3% **246**
	(±) 45% **247**	(±) 14% **248**

Scheme 71 – *N*-Arylation

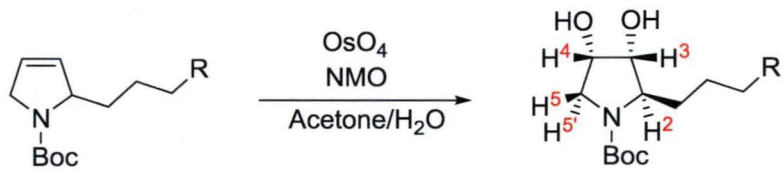
4.4 Dihydroxylations

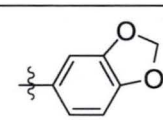
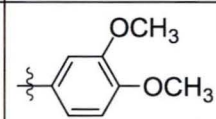
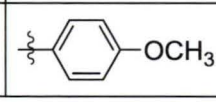
With the protected 3-pyrrolines in hand, dihydroxylation was employed to form the new analogues. The Upjohn method is one of the most common procedures which has been used widely for the dihydroxylation of alkenes and involves the use of osmium tetraoxide (OsO_4) as a catalyst with the co-oxidant *N*-methyl morpholin-*N*-

oxide (NMO).[137,138] Many modern syntheses manipulate this method to introduce a diol moiety into the target compound.[98,109,139,111] The co-oxidant, NMO enables the use of a catalytic amount of OsO_4, because this reagent is able to reoxidise the Os(VI) species to the active Os(VIII) species. While the pyrrolidines formed are racemic, there is the potential to form two different diastereomers. This method has shown to be highly diastereoselective with similar pyrroline substrates,[98,109,139,140,111,141] which is an important criterion, since the formation of diastereomers would limit the practicality of the method which provides rapid and efficient access to the target compounds.

N-Boc 3-pyrroline **243** was reacted with catalytic OsO_4 in the presences of NMO in acetone and water to give one product which was purified by column chromatography and characterised as the desired diol **249**. (Scheme 72) The ^1H NMR spectrum indicated the complete consumption of 3-pyrroline by the loss of multiplet at 5.6 ppm. Assignment of the product was made by analysis of the 2D-COSY (Figure 14) and HSQC spectra. From this, we assigned the methine at C4 (H^4) as the doublet of doublet resonating at 4.23 ppm, with coupling to the *cis*-methine at C3 (H^3) and the *cis* C5 (H^5) proton which is *trans* to the hydroxyl group. Also, the methine at C3 (H^3) resonated as a multiplet at 3.89 ppm with coupling to H^4 and H^2. The methine at C2 (H^2) resonated at as multiplet at 3.65 ppm, because of the presence of rotomers; no clear splitting pattern was observed. The methylene proton H^5 also resonated as a doublet of doublet at 3.5 ppm, showing the coupling with the adjacent methylene $H^{5'}$ at 3.40 ppm and the methine H^4. Interestingly, a weak correlation between the methylene $H^{5'}$ and the

methine H^2 was observed in the 2D-COSY spectrum, which is unexpected since they are four bonds from each other. Examination of the ^{13}C NMR spectrum also indicated the loss of the two alkenyl carbons at 125 and 130 ppm and the formation of two new signals at 75 and 79 ppm, which represent the two methines at C3 and C4. Mass spectroscopy gave the molecular ion 365 which is consistent with the introduction of the hydroxyl groups, forming dihydroxylated pyrrolidine **249** ($C_{19}H_{27}NO_6$ = 365 $gmol^{-1}$).



	R	% Yield
249		89%
250		62%
251		86%

Scheme 72 – Proposed Upjohn's dihydroxylation towards pyrrolidines

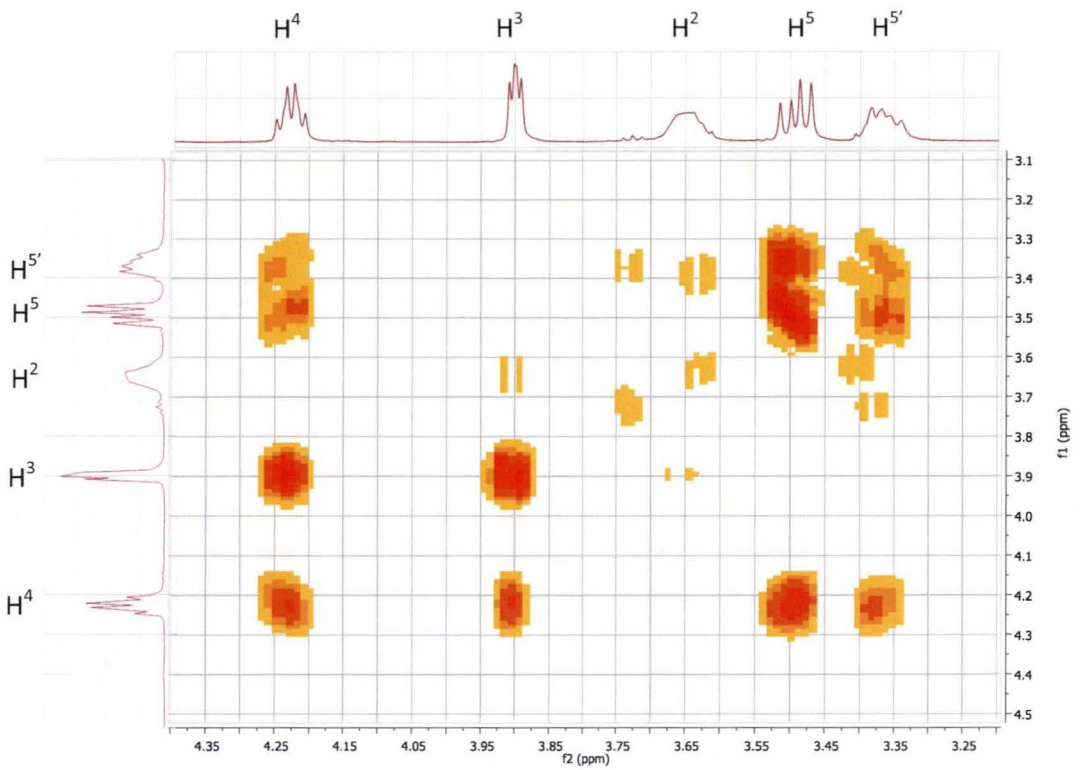


Figure 14 – 2D-COSY for dihydroxylated pyrrolidine **249**

Importantly, the above spectral data indicated that only a single isomer was formed, which appeared to be confirmed by 2D-NOESY experiment. 2D-NOESY and 2D-ROESY are the nuclear Overhauser effects, which provide information about cross relaxation through space proximity, and correlate protons that are close to each other.[142-144] In the example of pyrrolidine **249**, the 2D-NOESY spectrum showed the methine at C4 (H^4) correlated with the methine at C3 (H^3), indicating the *cis* diol, and the methylene at C5 which is *trans* to the hydroxyl group (H^5). The methine at C3 (H^3) only showed correlation with H^4, since the methine at C4 (H^4) is on the same face as H^3; whereas the methine at C2 (H^2) is on the opposite face to H^4 and H^3. Therefore this supports the formation of *cis*-3,4-dihydroxy pyrrolidine with the diol on the opposite face as the substituent at C2. The attack of the OsO_4 is

from the least stericly hindered face with the alkyl side-chain at C2 hindering the top face, and therefore, resulting in the one product as can be seen in following figure. (Figure 15) This finding was consistent with the corresponding diol derivatives.

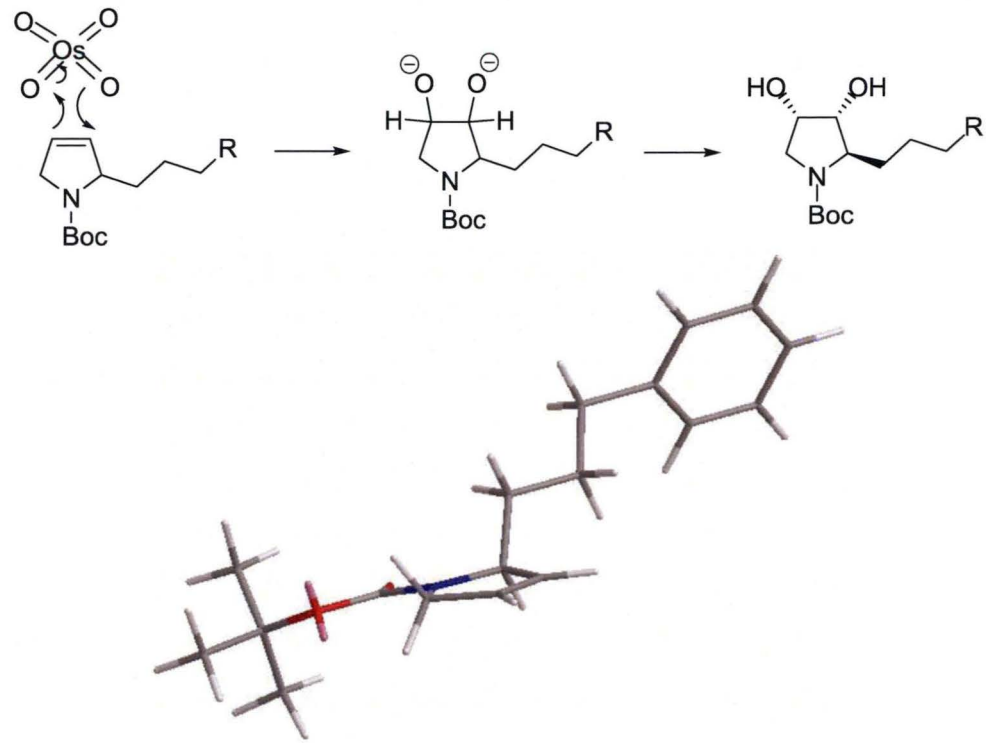
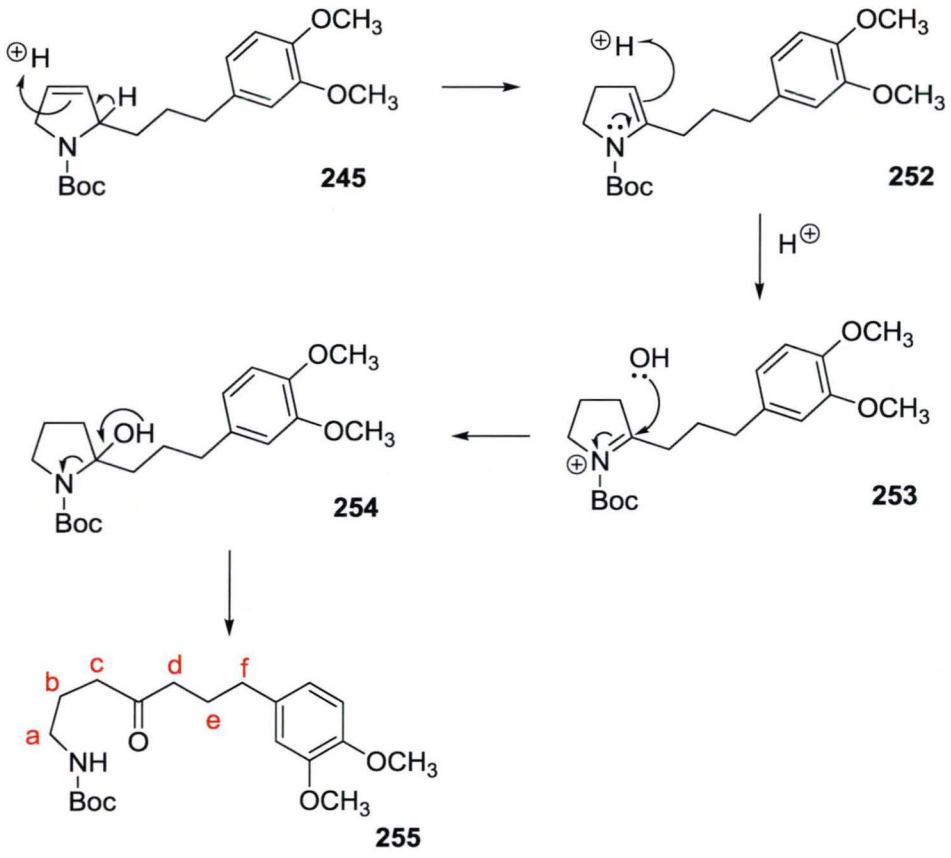


Figure 15 – Model analysis for dihydroxylation (R = Ph)

During the dihydroxylation of pyrroline **245**, one other new compound **255** was observed. The product was believed to be formed by isomerisation of the 3-pyrroline, followed by hydrolysis of the intermediate enamine **252,** to give the acyclic product **255**. A possible mechanism is proposed and shown in the following scheme which involves coordinating or protonation followed by a proton shift.[145,146]

(Scheme 73) However, it is not clear why this is the only substrate that appears to undergo the process.



Scheme 73 – Proposed Mechanism for pyrrole cleavage

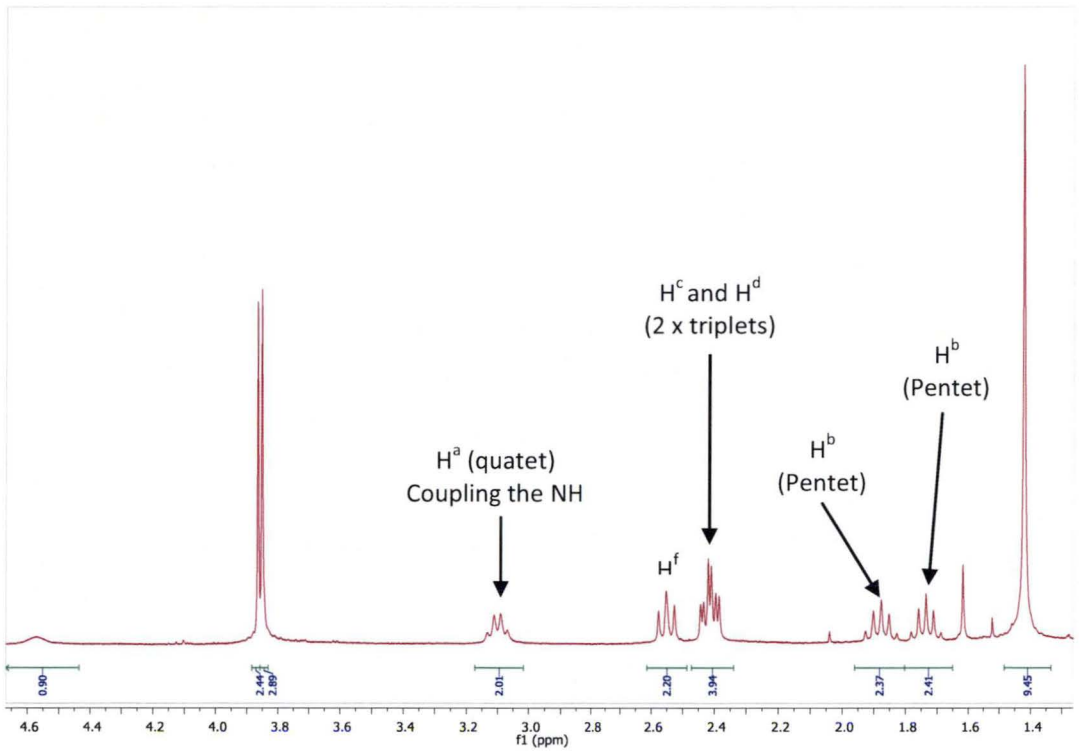


Figure 16 – NMR resonances for **255**

Spectroscopic analysis also supports the characterisation of the cleaved product **255** which was isolated in 12% yield. (Figure 16) In the aliphatic region of the ^{1}H NMR spectrum, the more complex resonances have disappeared. Despite the obvious broad N-*H* at 4.57ppm, and the singlets at 1.42, 3.85 and 3.86 ppm for the Boc and the two methoxy groups, they were replaced by two triplets overlapping and resonating at 2.41 ppm representing the methylene group adjacent the ketone group. A quartet at 3.10 ppm represents H^a due to the deshielding effect from the Boc group, therefore the resonance lies further downfield. An apparent triplet resonates at 2.55 ppm for H^f, as well as the two pentets at 1.75 and 1.88 ppm for H^e and H^b respectively. More importantly, no pyrrolidine peaks and twelve aliphatic protons were observed. Manipulating the ^{13}C-DEPT NMR spectrum indicates that there are six methylene carbons in the aliphatic region from 24.16 to 42.11 ppm,

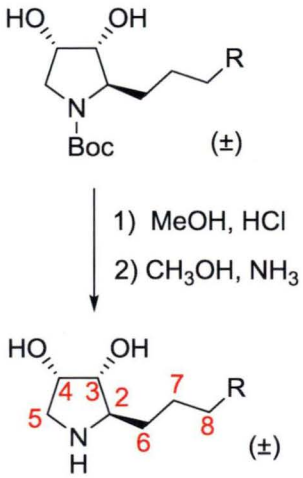
which confirms the loss of the methane for C2 of the pyrrolidine. The presence of a typical aliphatic ketone resonance at 219 ppm, as well as the IR spectrum which shows a strong sharp peak at 1710 cm^{-1} confirms the formation of a ketone. Mass spectroscopy gave the molecular ion 365, supporting the formation of the ring-opened product **255**.

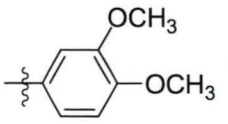
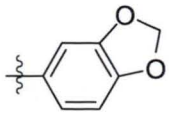
Although the analyses of the protected pyrrolidine were clear, the protecting group was removed to eliminate rotomers and to obtain the target pyrrolidine analogues.

4.5 Deprotection

The last step in the sequence towards the target pyrrolidines was the removal of the Boc-protecting group. As previously demonstrated in the synthesis of proline derivatives, Boc can be removed under acidic conditions. Therefore, *N*-Boc pyrrolidines were treated with methanolic HCl under the same conditions as previously described to yield the crude pyrrolidines as the HCl salt. It was readily purified by column chromatography on silica gel with an eluent of dichloromethane / methanol / ammonia, and gave the dihydroxy pyrrolidines as the free amine in good yield. (Scheme 74) The ^{1}H NMR spectrum was much easier to interpret due to the absence of rotomers and the loss of singlet at 1.38 ppm which confirmed the removal of the Boc protecting group. Analysis of the ^{1}H and ^{13}C NMR spectra, as well as the 2D-COSY and HSQC spectra of the isolated pyrrolidine **256,** supported the formation of the desired product. The ^{1}H NMR spectrum showed a multiplet at 4.25 ppm for the methine at C4 and a doublet of doublets at 3.92 ppm for the

methines proton at C3 due to first order coupling with the methine at C4 and C2. The methine at C2 overlapped with one of the methylene protons of C5, which resonated as a multiplet at 3.4 ppm. A doublet of doublet at 3.92 ppm represented the other methylene proton at C5. The aliphatic protons from the alkane chain also showed at multiplets at 2.5 and 1.7 ppm with an integration ratio of two and four respectively. Analysis of the ^{13}C NMR spectrum also showed the loss of a signal at 28.53 ppm for the Boc group and gives only nine aliphatic carbon signals, including the two methoxy groups at 27.7, 29.2, 34.2, 49.0, 55.7, 55.8, 60.6, 69.4 and 74.9 ppm. The HSQC indicated resonances at 74.9 and 69.3 ppm, representing the oxymethines at C3 and C4 respectively. The desired pyrrolidine was also confirmed by mass spectroscopy with a molecular ion of 281 supporting the molecular formula of $C_{15}H_{23}NO_4$. The spectral data for **256** was similar to **257** except for the methylenedioxy resonances.



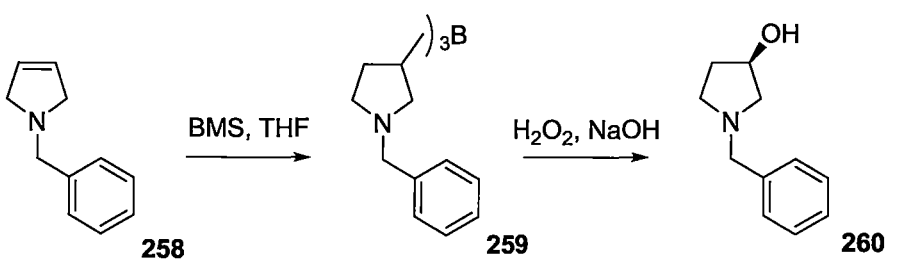
	R	Yield
256		(±) 78%
257		(±) 67%

Scheme 74 – Deprotection

The methodology for the formation of 3-pyrroline scaffolds has therefore been successfully demonstrated by exploiting the partial reduction as a key step. Using this strategy, the synthesis of analogues of pyrrolidine natural product has been achieved in 6 steps.

4.6 Monohydroxylation

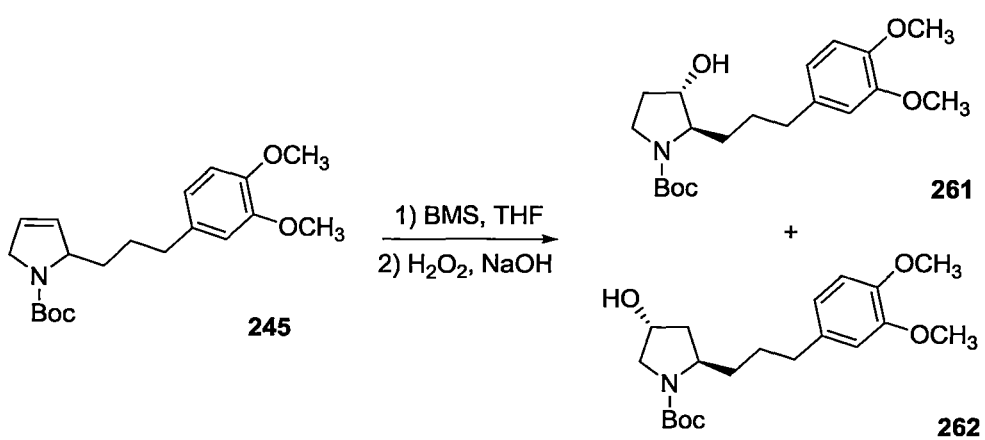
Some naturally occurring compounds contain only one hydroxyl group on the pyrrolidine ring, such as preussin (**101**). Therefore with the three-carbon spaced 3-pyrroline scaffold in hand, monohydroxylation was also investigated. Brown demonstrated the hydroboration of pyrroline **258** with borane-methyl sulfide (BMS) to give the borane **259**. This intermediate borane was then oxidised with alkaline hydrogen peroxide to give *N*-benzyl-3-pyrrolidinol **260** in quantitative yield.[147-149] (Scheme 75)



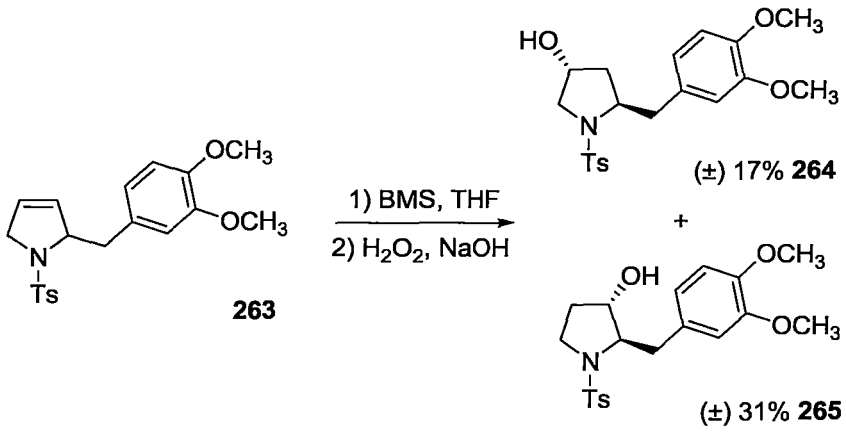
Scheme 75 – Hydroboration

Thus the N-Boc 3-pyrroline **245** reacted with 1.5 equivalents of BMS, and oxidised with a 3:1 mixture of 6M sodium hydroxide / hydrogen peroxide as per the method of Brown.[147] (Scheme 76) After column chromatography, an inseparable 1:1 mixture of two products was observed in 82% combined yield. Assignment by ^{1}H NMR spectroscopy was difficult due to the presence of rotomers, yet the

compounds were assigned as the products of 3-hydroxyl **261** and 4-hydroxyl **262** pyrrolidines. This is because the resonances for the methine at C3 for **262** and C4 for **261**, at 4.30 and 4.10 ppm were consistent with the attachment of a hydroxyl group. Also the presence of the multiplets at 3.40 ppm and 3.65 ppm indicate the methine at C2 for both **261** and **262**, respectively. Mass spectroscopy of the mixture showed a molecular ion of 365 $gmol^{-1}$ and was consistent with the formula of $C_{20}H_{31}NO_5$ for monohydroxylation. Due to the lack of steric bias of the alkene, it is surprising that the two compounds were formed. However, the hydroxylation was expected to be facially selective. This result is consistent with research on a similar substrate within the Smith group which showed that monohydroxylation under the same conditions gave two mono-hydroxylated pyrrolines, *trans*-C4 **264** and *trans*-C3-**265** and that were separable by column chromatography.[150] (Scheme 77) The relative stereochemistry of **265** was also confirmed by X-ray crystallography. Due to the complexity observed in the ^1H NMR spectrum, Boc should be removed for the elimination of rotomers for further product analysis.



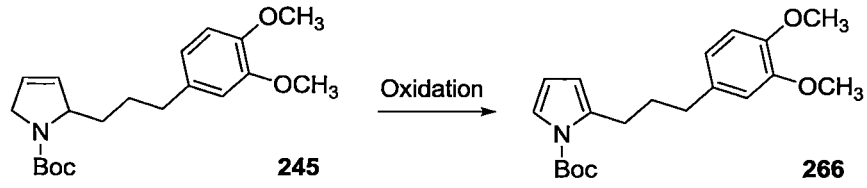
Scheme 76 – Monohydroxylation



Scheme 77 – Monohydroxylation of one-carbon spaced pyrroline

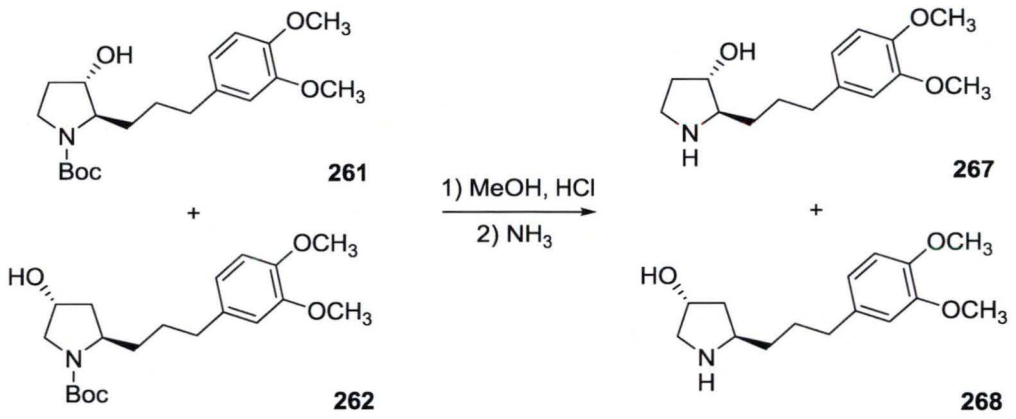
Interestingly the ring cleaved side product **255**, the same product isolated after the dihydroxylation, was also isolated from the reaction mixture. Brown also reported ring cleavage from the reaction of the *N*-benzyl-3-pyrroline which was caused by allylic amine isomerisation from the amine-borane complex.[147] However, it was not expected for the Boc-protected amine because no complex with borane is formed.

During the isolation of the monohydroxylation products, pyrrole **266** was also obtained in 5% yield. It was presumed to have arisen during the oxidation of the borane intermediate from traces of the unreacted 3-pyrroline. (Scheme 78) This assignment was supported by the ^{1}H NMR spectrum with the characteristic pyrrolic proton resonances at 7.18, 6.06 and 5.70 ppm. The aliphatic protons also resonated as two triplets and a pentet at 2.88, 2.64 and 1.93 ppm respectively which supported the loss of the C2-methine of the pyrrole. Examination of the ^{13}C NMR spectrum also indicated only three signals at 29.08, 31.26 and 35.74 ppm, representing the three aliphatic carbons on the side-chain with six aromatic methines.



Scheme 78 – Tautormerisation of pyrroline **245**

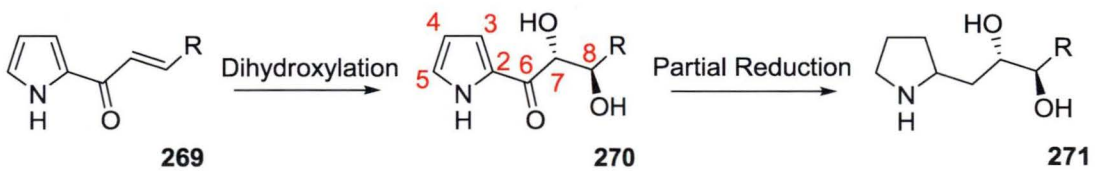
Boc deprotection of the mixture of monohydroxylated pyrrolidines **261** and **262** was performed under the standard conditions as previously described and gave the pyrrolidines as the HCl salt. (Scheme 79) After purification on silica gel, the ^{1}H NMR indicated an obvious loss of the singlet at 1.44 ppm representing the loss of the Boc group. The assignment from 2D-COSY indicated the two multiplets resonating at 4.50 and 4.20 ppm which indicated the methine at C3 for **267** and the methine at C4 for **268**. One of the methines at C2 for either **267** or **268** resonated as a multiplet at 3.55 ppm, while the other overlapped with the methylene protons of the pyrrolidine. However, the analysis of the mixture was not easy due to overlapping resonances in the aliphatic region. Examination of the ^{13}C NMR spectrum showed fourteen signals in the aliphatic region from 29.02 to 76.38 ppm for the 1:1 mixture of the combined products. Due to the inability to separate the products and the analysis of mixtures, no further mono-hydroxylations were attempted.



Scheme 79 – Boc deprotection

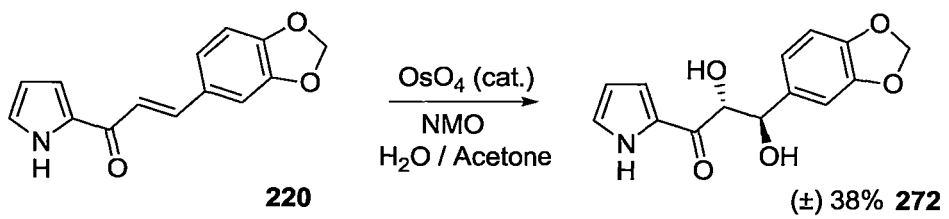
4.7 Dihydroxylation of α,β-unsaturated ketopyrrole

The aldol product yielded as a α,β-unsaturated ketone which itself is a functional group that could be exploited for the introduction of substituents onto the side-chain. Therefore a modified side-chain could provide a beneficial addition to the developed synthesis towards peptide formations and drugs development. The dihydroxylation of the alkene of α,β-unsaturated ketopyrroles **269** before formation of the 3-pyrroline, would yield side-chain C7 and C8 dihydroxylated analogues **271**. Compounds of this type have not been reported previously, and due to the proposed methodology the structural analogues could be accessed. (Scheme 80)



Scheme 80 – Proposed synthesis

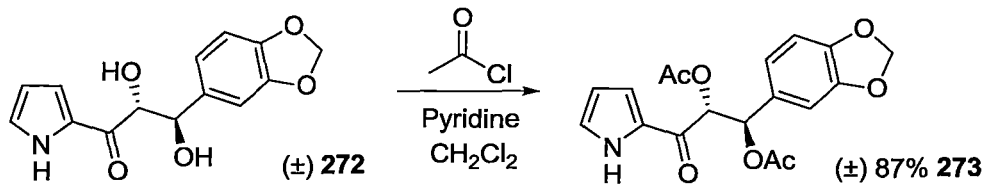
To test this, pyrroline **220** was treated with OsO_4 and NMO under the standard conditions with the addition of column chromatography. The product **272** was isolated in 38% yield. (Scheme 81) The diol was identified by ^1H NMR spectroscopy, with the spectrum showing the loss of the alkene and the presence of two doublets at 4.82 and 4.90 ppm, coupling constants of 3.6 Hz, representing the methine protons of the side-chain. Examination of the ^{13}C NMR spectrum also shows the two carbons with oxygen attached, resonating at 70.03 and 68.29 ppm.



Scheme 81 – Dihydroxylation of the α,β-unsaturated ketopyrrole

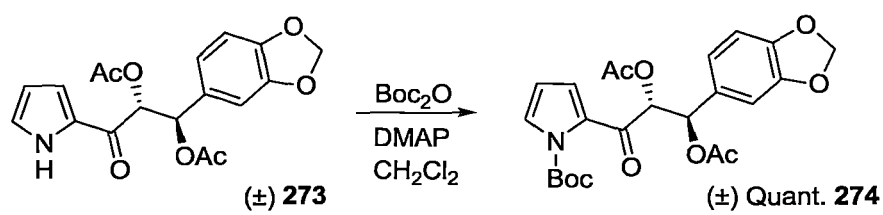
Ketopyrrole **272** was subjected to partial reduction using the zinc / HCl conditions as previously described. However, the ^1H NMR spectrum of the crude mixture only showed decomposition of the starting material with no clear product formed. It was postulated that the hydroxyl groups may not be stable under the harsh conditions, therefore protection is required. Compound **272** reacted with 2.4 equivalents of acetyl chloride in the presence of pyridine[136] to give the isolated, protected ketopyrrole **273** in 87% yield. (Scheme 82) The ^1H NMR spectrum showed two new singlets at 2.01 and 2.10 ppm for the two methyl protons for the acetyl groups. The doublets for the methine protons were shifted to 5.83 and 6.29 ppm. Acetylation was also selective for the hydroxyl groups as the broad singlet at 9.95

ppm indicated the N-*H* is still present. Examination of the ^{13}C NMR spectrum also shows new resonances at 20.74 and 20.95 ppm and at 169.6 and 169.9 ppm for the two carbonyl groups, indicating the presence of both the acetyl groups.



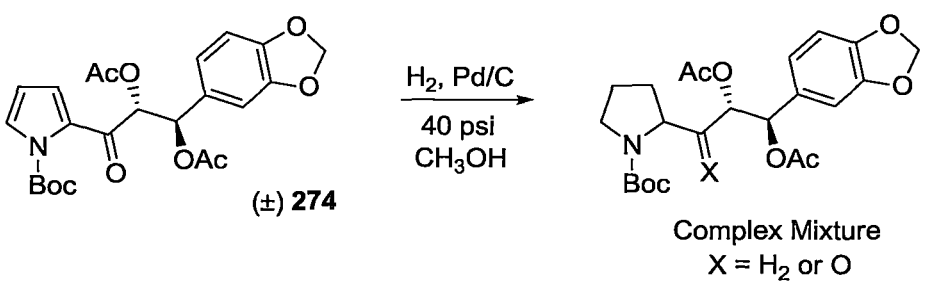
Scheme 82 – Acetylation

When the protected diol **273** was subjected to Zn / HCl reduction under the same conditions, examination of the ^{1}H NMR spectrum of the crude material again only showed decomposition starting material. The cause of this reaction may also be due to the harsh reduction conditions. As an alternate synthetic pathway, pyrroles could be reduced under catalytic hydrogenation as previously described, which would yield the saturated pyrrolidine. Hence, the keto pyrrole **273** was activated by the introduction of a Boc group using the standard methods to give ketopyrrole **274** in quantitative yield. (Scheme 83) Examination of the ^{1}H NMR spectrum indicated the presence of the Boc group by the singlet at 1.55 ppm, the loss of N-*H* and the coupling to the three pyrrolic protons.



Scheme 83 – Activation

The activated pyrrole **274** was subjected to catalytic hydrogenation under standard conditions. During this time the starting material was consumed. (Scheme 84) The ^{1}H NMR spectrum and TLC of the crude product indicated numerous product formations. Pruification of the product was attempted on silica gel, however only 10% of the unreacted starting material was obtained. Unlike the pyrrole-2-carboxylates, the carbonyl can also be reduced, which may complete the system. Different catalysts or alternate reduction methods are therefore required for the efficient hydrogenation of the 2-ketopyrroles. However this was not investigated further.



Scheme 84 – Catalytic Hydrogenation

4.8 Conclusion

In this chapter, we have successfully demonstrated the formation of pyrroles as scaffolds towards drug-like molecules in five short steps in good overall yield, using the partial reduction of pyrrole as a key step. This synthetic pathway has been demonstrated practically for the formation of 3-pyrroline scaffolds, and they have been further functionalised by *cis*-dihydroxylation. This synthetic intermediate could be modified or extended further for numerous other useful analogues through selective manipulation of the alkene in the 3-pyrroline intermediates. This

could include hydroboration, amino hydroxylation or Heck acylation,[151] amongst other methods and highlights the potential value of 3-pyrrolines scaffolds.

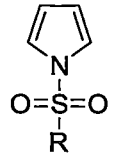
Chapter 5

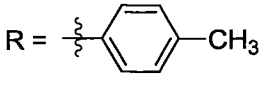
Two-Carbon Spaced Pyrrolidine Alkaloid Analogues

5.1 Introduction

During the investigations of the hydroxylated pyrrolidines, many natural and synthetic compounds containing an aryl and a pyrrolidine ring separated by one-carbon, such as anisomycin (**99**), have been reported.[3,105] Kim reported the synthesis of side-chain extended analogues of anisomycin. Their synthetic approach was not the most practical to adopt for multiple targets as previously described.[106] With the reduction of pyrroles being effective for the formation of the three-carbon spaced pyrrolidines, we now report the partial reduction of pyrroles for the formation of two-carbon spaced pyrrolidines.

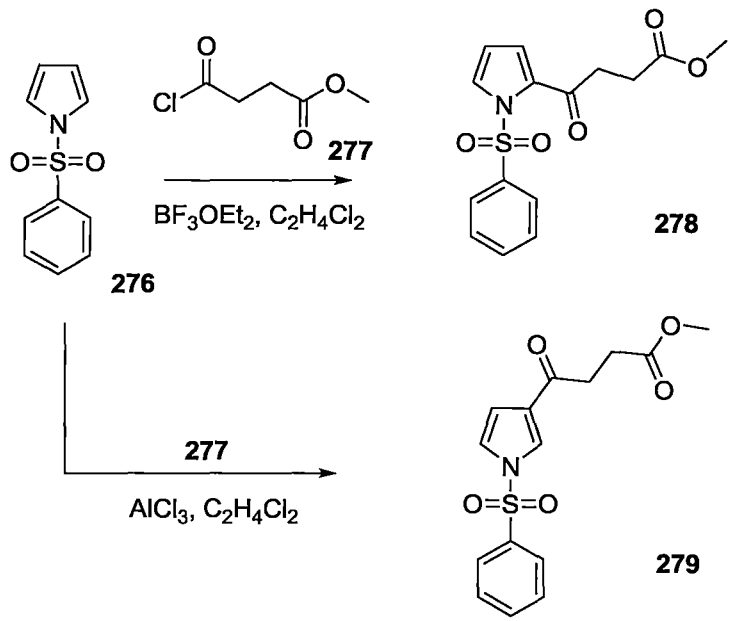
The construction of the α-keto pyrrole as the carbon skeleton is an essential step in synthetic schemes, while the synthesis for the three-carbon spaced pyrrolidines uses aldol chemistry to form the carbon skeleton. This is not possible for systems with one less carbon. Previous experience within the group has shown that *N-p*-toluenesulfonyl pyrrole (*N*-tosylpyrrole (**275**)) is an excellent template for the preparation of the α-ketopyrrole reduction precursors for two key reasons. The first is that *N*-sulfonylpyrroles have been shown to be reduced to pyrrolines under relatively mild conditions, initially by Ketcha and later by the Smith group.[116,117] The second is that the pyrrole nucleus can be substituted readily to introduce the desired side-chain.





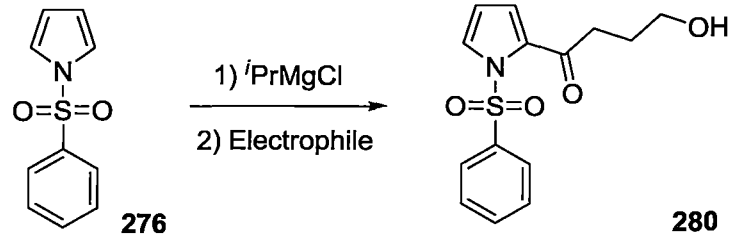
275

Kakushima demonstrated that acylation can take place selectively at either C2 or C3 on *N*-sulfonyl pyrroles **276** with an acid chloride and a Lewis acid. Milder Lewis acids such as $BF_3.OEt_2$ promote the formation of the 2-substituted pyrrole **278**, while 3-substituted pyrroles **279** can be obtained using $AlCl_3$ promoted condtions.[152] (Scheme 85)



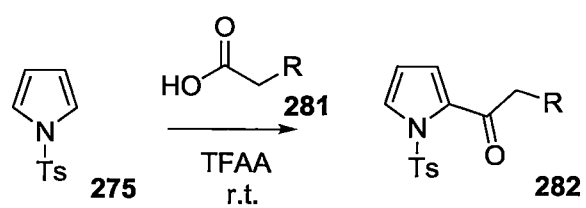
Scheme 85 – *N*-sulfony Acylations

One of the most common methods reported for substitution at the 2-position of unsubstituted *N*-sulfonylpyrrole is *via ortho*-metalation. For example, Ginsmore and co-workers demonstrated 2-substituted-*N*-tosyl pyrroles **280** can be obtained *via ortho*-metalation with a Grignard reagent, followed by reaction with an electrophile including esters and lactones to give the desired α-ketopyrrole.[153] (Scheme 86)



Scheme 86 – Acylation *via* Gringnard Reagent

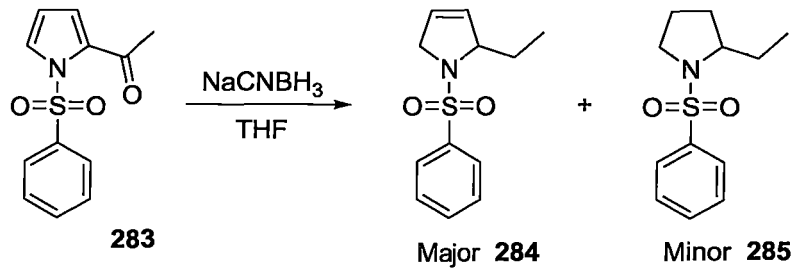
Knight has demonstrated that regioselective acyl substitution takes place selectively on *N*-tosyl pyrroles **275** directly from a carboxylic acid **281** by reaction with trifluoroacetic anhydride (TFAA).[154] (Scheme 87) The reaction occurs selectively to give the 2-acyl derivatives **282** in high yield under relatively mild conditions and has been used previously within the Smith group.[117] The mechanism was assumed to be the formation of a mixed anhydride with TFAA and the reacting carboxylic acid.[155] This method is much more attractive as it does not require the formation of an acid chloride or metallation of the pyrrole.



Scheme 87 – Acylation with TFAA Acid

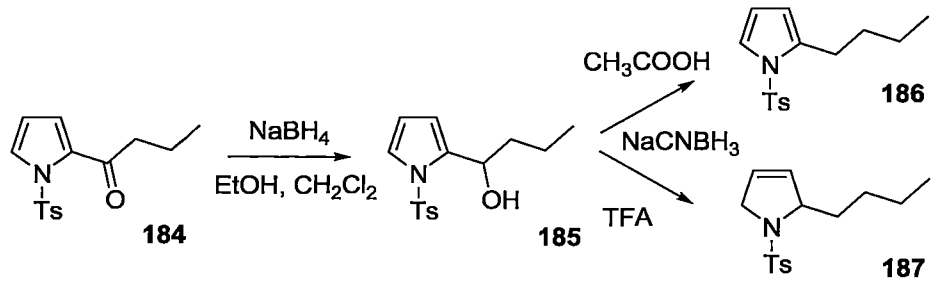
Using the appropriate acid derivatives, such as substituted phenyl acetic acid (many of the alkoxy derivatives are commercially available) would yield the corresponding carbon skeleton with a 2-carbon-spacer between the aryl and the pyrrole rings. With the skeleton formed, the partial reduction using sodium cyanoborohydride ($NaCNBH_3$) in trifluoroacetic acid (TFA), initially reported by Ketcha,[116] would give

the corresponding 3-pyrroline **284**. (Scheme 88) In the previous work protection of the amine is required prior to dihydroxylation. However, the use of *N*-sulfonyl pyrroles for the reduction gives a built-in *N*-protection group. *N*-Sulfonyl groups can then be removed by dissolving metal reduction.[156,157]



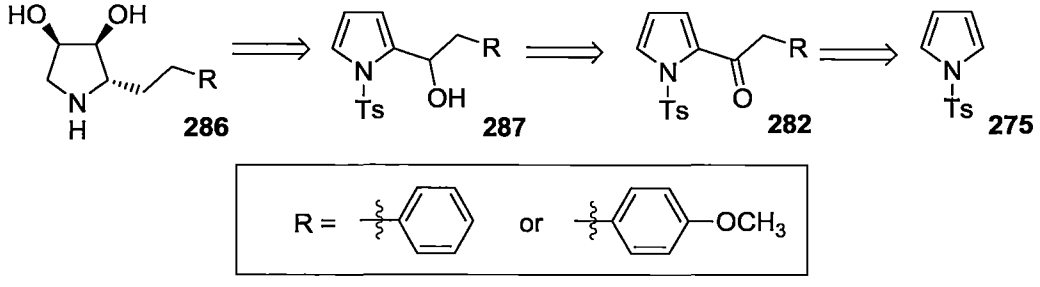
Scheme 88 – Ketcha's reduction of *N*-phenyl sulfonyl pyrroles with $NaCNBH_3$ in TFA

The method for partial reduction reported by Ketcha is the key step in the synthesis. Previous work within the group has investigated the partial reduction and developed a more practical two-step reduction method.[117] (Scheme 89) This involves the initial reduction of *N*-tosyl-α-keto pyrrole **184** with sodium borohydride ($NaBH_4$) to give the relatively stable alcohol **185** before further reduction to the 3-pyrroline **187**, using sodium cyanoborohydride ($NaBH_3CN$) in TFA. This method required fewer equivalents of sodium cyanoborohydride and TFA, and gave higher and consistent product yields. It was shown that the reduction of the ketone is the rate limiting step, and proceeds faster using sodium borohydride.



Scheme 89 – Partial reduction *via* sodium hydride sources

Another advantage of the intermediate alcohol is that the reduction outcome can be controlled by the choice of solvents; for example, by changing to acetic acid instead of the stronger acid TFA, the reaction gave the 2-alkylpyrroles **186**. The advantage of this is that a second substituent could then be introduced at C5 using the same protocol. Therefore, due to the ease in the formation of the 2-acyl derivatives and mild partial reduction, *N*-toluenesulfonyl pyrrole **275** will be used as a template towards the two-carbon linked pyrrolidines **286**. (Scheme 90)

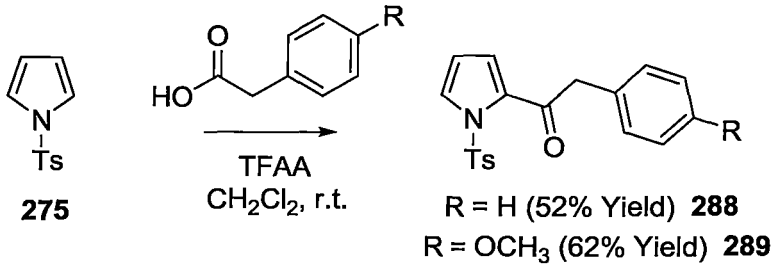


Scheme 90 – Proposed synthetic scheme for two-carbon spaced pyrrolidines

5.2 Formation of N-sulfonyl-pyrrolines

N-Toluenesulfonylpyrrole **275** was previously prepared by the Smith group, and was obtained by the reaction of pyrrole and tosyl chloride with solid sodium hydroxide

in dichloromethane by the method of Zonta.[158] **275** reacted with phenylacetic acid and trifluoroacetic anhydride (TFAA) in dichloromethane at room temperature and gave the desired product **288** in 52% yield after purification by column chromatography. (Scheme 91) The yields are typically higher for this reaction but it was not optimised due to sufficient material being obtained. It has been shown that heating can increase yields. [154,155]

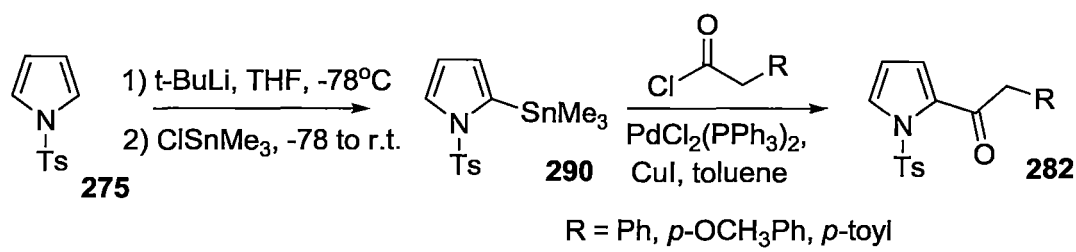


Scheme 91 – Formation of *N*-sulfonyl pyrrolines

Examination of the ^1H NMR spectrum indicated the addition of the aryl groups by the multiplet at 7.02 ppm and the new singlet at 3.96 ppm with an integration ratio for two protons representing the methylene on the side chain. The pyrrolic proton splitting also changed and confirmed the unsymmetrical pyrrole but two of the pyrrolic protons appeared as doublet of doublets at 7.07 and 7.79 ppm, and the other as a multiplet at 6.30 ppm. The ^{13}C NMR spectrum also indicated the presence of the C=O peak at 198.4 ppm, an indication of ketone, and the methylene carbon at 46.6 ppm. The characterisation not only confirms the formation of the 2-acyl *N*-toluenesulfonylpyrrole **288**, but also that the reaction occurred at C2. If the substitution took place at C3 the pyrrolic proton at C2 would be expected to resonate at ~8 ppm.

The reaction with *p*-methoxyphenylacetic acid under the same conditions gave the corresponding α-ketopyrrole **289** in 62% yield. The compound was also characterised by spectroscopic analysis and displayed the same key features.

The spectral data was also consistent with similar compounds reported in literature, which was prepared from *N*-tosylpyrroles **275** *via* 2-lithiation. The lithio intermediate was then transformed into the 2-trimethylstannylpyrroles derivative **290** followed by Pd(0) catalysed cross-coupling with phenylacetyl chloride to yield the 2-acyl *N*-toluenesulfonylpyrrole derivatives **282**.[159] (Scheme 92)

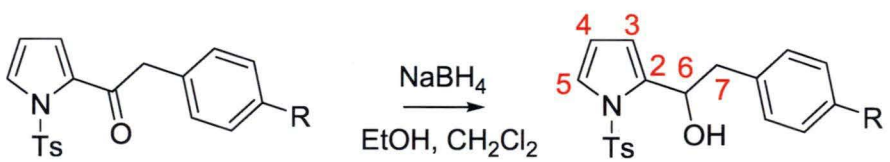


Scheme 92 – Formation of *N*-tosylpyrroles *via* 2-lithiation

5.3 Selective Partial Reduction

As mentioned in the previous chapter, the reduction of the carbonyl group is the rate limiting step. Therefore the alternative two-step reduction developed by You was applied.[117] *N*-Tosyl α-keto pyrrole **288** was reacted with sodium borohydride in a mixture of dichloromethane and ethanol at room temperature to give the expected alcohol **291** in 93% yield after purification by column chromatography. (Scheme 93) Examination of the ^{1}H NMR spectrum showed the obvious broad singlet at 2.71 ppm representing the presence of the alcohol with the methine at

C6, resonating as a doublet of doublets at 5.17 ppm. This was coupled to the methylene protons at 3.01 and 3.16 ppm, which also gave two signals since they are diastereotopic. The ^{13}C NMR spectrum also showed a loss of the carbonyl carbon signal at 198.4 ppm, and a new resonance in the aliphatic region at 66.81 ppm for C6. The reduction was also supported by the IR spectroscopic data which showed the loss of the C=O signal at 1675 cm^{-1}, and a new stretch at 3556 cm^{-1} representing the alcohol. A similar result was obtained for the reduction of the *p*-methoxy derivative **292**. It is worth noting that α-hydroxypyrroles are typically unstable as they readily lose water as a feature showed in the zinc reduction. However, due to the *N*-sulfonyl group withdrawing electron density from the nitrogen, they are very stable and can be stored.

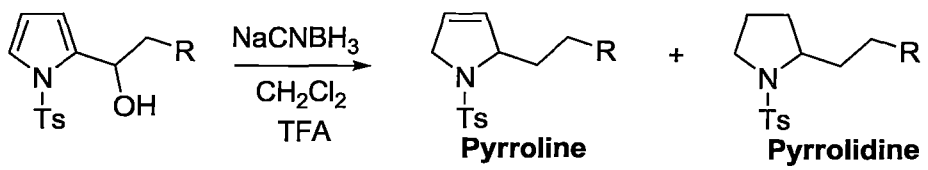


R = H (93%) **291**
R = OCH_3 (89%) **292**

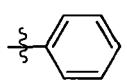
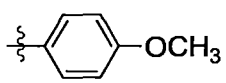
Scheme 93 – Reduction of *N*-sulfonyl ketopyrroles

The stable alcohols were then reacted with $NaBH_3CN$ in a mixture of dichloromethane and TFA at room temperature and after column chromatography obtained in quantitative yields. (Scheme 94) Examination of the ^{1}H NMR spectrum indicated the major product was the desired pyrroline **293**. The multiplet at 5.50 ppm represents the two alkene protons of the 3-pyrroline protons at C3 and C4, and was consistent with these reported systems.[160] However, the major resonances also overlapped with the fully reduced pyrroline **294** in a 3:1 ratio by the comparison of

the aliphatic carbon signals, as this was clearly observed in the ^{13}C NMR spectrum by the extra seven aliphatic carbons signals between 21.64 to 59.94 ppm. Unfortunately, the mixture of compounds was inseparable unlike the *N*-Boc derivatives. The *p*-methoxy derivative gave the 3-pyrroline **295** and the saturated pyrrolidine **296** in a 4:1 ratio.



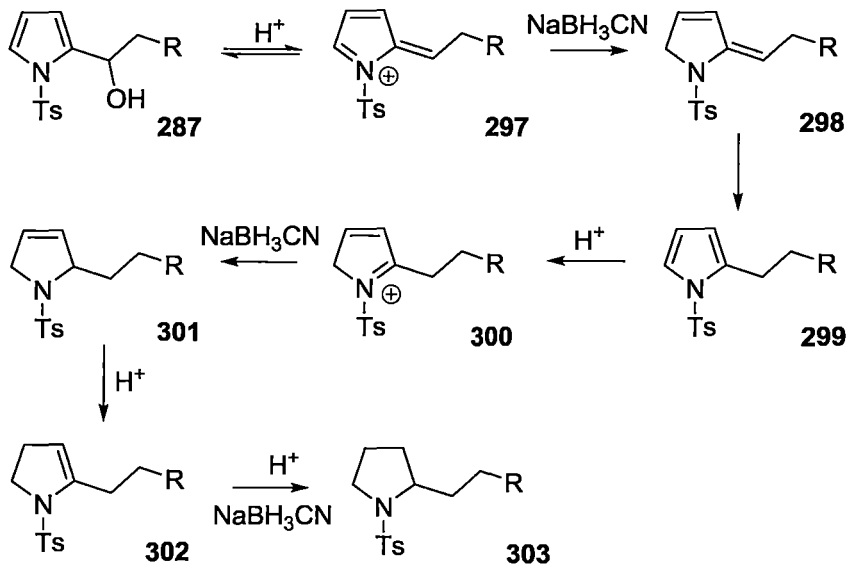
Inseparable

R	**Pyrroline**	**Pyrrolidine**	% Yield	Pyrroline vs Pyrrolidine
	**293**	**294**	Quantitative	3:1
	**295**	**296**	Quantitative	4:1

Scheme 94 – Partial Reduction *via* $NaCNBH_3$

This over-reduction has been reported in the original reference by Ketcha, but was a surprise as the method of You only observed this over-reduction in small amounts in a few examples.[117,116] The reduction mechanism was postulated as shown in scheme 95, in which protonation of the alcohol and dehydration forms a conjugated pyrrolenium ion **297**, which is reduced with sodium cyanoborohydride. Tautomerisation forms the *N*-sulfonyl pyrrole **299**. Protonation from the strong acid source on C5 allows the formation of a second pyrrolenium ion **300.** Further reduction gives the over-reduced *N*-sulfonyl pyrrolidine **303** by the reduction of the pyrrolenium ion to give an enamine, followed by further protonation and reduction.

During the investigation, it was noted that the formation of the over-reduced pyrrolidines could be limited by controlling the number of equivalents of sodium borohydride. However a small amount of the fully reduced pyrrolidine was still formed. Nevertheless, the mixtures were subjected to the following steps where separations could be possible.

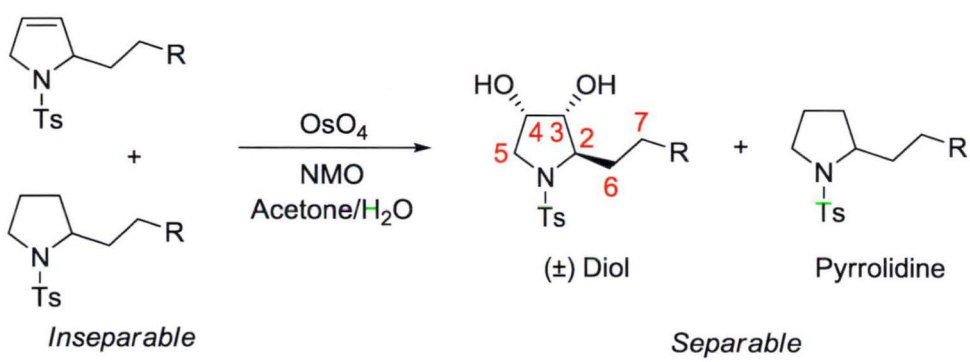


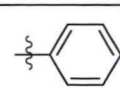
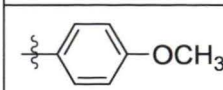
Scheme 95 – Mechanism of over-reduction

5.4 Dihydroxylation

The Upjohn method was shown to be successful for the dihydroxylation of the 3-pyrroline scaffolds with high levels of diastereoselectivity. Therefore, to complete the two-carbon spaced pyrrolidines, the impure 3-pyrrolines were reacted under the same conditions as the *N*-Boc-pyrrolines, with catalytic OsO_4 in the presence of NMO, acetone and water. (Scheme 96) As expected, the desired diol products **304** and **306** were isolated but in lower than expected yields of 43% to 46%, although this is effectively over-2-steps. The structure was assigned by analyses of ^{1}H, ^{13}C

NMR, 2D-COSY and 2D-HSQC spectroscopy. In compound **306**, the multiplets at 4.23 and 3.91 ppm represent the methines at C4 and C3, respectively. The methylene at C5 resonated as two sets of doublet of doublets at 3.12 and 3.57 ppm with coupling to the methine at C4. The methine at C2 resonated as a triplet of doublets at 3.45 ppm as expected, due to the coupling with the methylene at C6 and the methine at C3. Examination of the ^{13}C NMR spectrum also indicated the loss of the alkene carbons and the presence of the two carbons attached to oxygen at 75.47 and 70.09 ppm. Mass spectroscopy also confirmed the presence of the hydroxyl groups by the molecular ion at 391 consistent with the formula $C_{20}H_{25}NO_5S$. The phenyl derivative **304** showed the same spectroscopic features. Only one diastereomer was formed and the product was believed to be the same as the three-carbon spaced derivatives with the hydroxyl groups introduced on the less steric hindered face or *trans* to the substituent at C2.



R	Diol (% Yield)*	Pyrrolidine (% Yield)*
	(±) 43% **304**	17% **294**
	(±) 46% **306**	14% **296**

* Over-2-steps

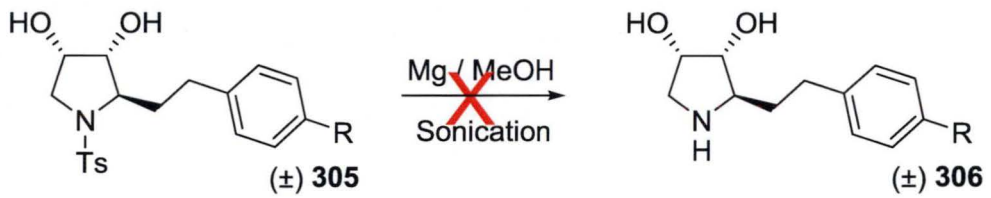
Scheme 96 – Dihydroxylation

The saturated *N*-sulfonyl pyrrolidines **294** and **296** were also isolated as expected in 17% and 14% yields respectively. (Scheme 96) Examination of the ^{1}H NMR spectrum of **305** showed the aliphatic protons resonating as multiplets at the aliphatic region from 1.41 to 3.61 ppm, while the ^{13}C NMR spectrum showed the seven signals resonated at 20.76, 23.34, 30.01, 31.62, 36.95, 48.32, and 59.05 ppm, representing the seven aliphatic carbons including the methyl group from the *N*-toluenesulfonyl group. Mass spectroscopy also gave a molecular ion 329 $gmol^{-1}$ and was consistent with the saturated product. The spectral data for pyrrolidine **305** was consistent with that reported in literature,[161] which supports the formation of the fully saturated pyrrolidine.

5.5 Desulfonylation

With the hydroxyl group introduced, the last step is the removal of the *N*-toluenesulfonyl group. This can be achieved *via* dissolving metal reduction.[156,157,117] Ragnarsson reported a mild and efficient method for the removal of *N*-phenylsulfonyl group using magnesium in methanol under ultrasonic conditions,[156] which is a method used successfully in the Smith group.[117,150] To complete the synthesis of the two-carbon spaced pyrrolidines, the dihydroxylated pyrrolidines reacted with 20 equivalents of magnesium turnings in methanol under ultrasonic conditions for 6 h. (Scheme 97) The mixture was concentrated under reduced pressure and filtered through a thin layer of Celite and washed with ammonia. However, the ^{1}H and ^{13}C NMR spectra of the crude mixture only indicated the isolation of the starting material. Preparing freshly activated

magnesium also failed to result in deprotection, even with extended reaction time. It is not clear why deprotection failed but because of time constraints, no further methods were attempted. However if required, sodium metal in liquid ammonia or sodium naphthalenide could achieve reactions.[162,163]



Scheme 97 – Desulfonylation

5.6 Conclusion

This methodology has demonstrated the use of *N*-sulfonylpyrroles as a template for the regioselective substitutions and partial reductions of the pyrrole core to form 3-pyrrolines. Although the desulfonated pyrrolidines could not be obtained from this primary investigation, *N*-toluenesulfonyl pyrrole was demonstrated as a template for the synthesis of two-carbon spaced pyrrolidines *via* distereoselective dihydroxylation. This synthesis allowed rapid construction of building blocks for the synthesis of compounds related to the pyrrolidine natural products, such as anisomycin and may find applications for the synthesis of compound libraries.

More importantly, we have demonstrated the use of pyrrole as a template for the rapid synthesis on a carbon skeleton before partial reduction and further introduction of substituents onto the pyrrolidine ring. This methodology has the

potential for application in drug development and for the synthesis of novel compounds for the evaluation of biological activities, as they are in chemical space where little chemistry or biology is known.

Part III

Experimental

Nuclear Magnetic Resonance (NMR) Spectroscopy

Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance spectra were completed on a Varian Mercury 2000 Spectrometer operating at 300 MHz and 75 MHz respectively. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were obtained in deuterated chloroform ($CDCl_3$), unless otherwise stated.

Where ^{1}H NMR spectra were recorded in deuterated chloroform ($CDCl_3$) the peak due to residual chloroform ($CHCl_3$) was referenced to δ 7.26 ppm. Where spectra were recorded in deuterated acetone (d_6-Acetone) the peak due to residual acetone was referenced to δ 2.09 ppm. Where spectra were recorded in deuterium oxide (D_2O) the peak due to residual water was referenced to δ 4.79 ppm. Where spectra were recorded in deuterated methanol (CD_3OD) the peak due to the residual methanol (CH_3OH) was referenced to δ 3.31 ppm.

^{1}H NMR data are reported as follows: chemical shift, multiplicity, relative integral and coupling constant *J* (Hz). Multiplicity assignments have been abbreviated as follows: s = singlet, d = doublet, t = triplet, m = mulitplet, a = apparent, b = board.

Where proton-decoupled ^{13}C spectra were recorded in $CDCl_3$ the central peak was referenced to δ 77.16 ppm, where spectra were recorded in d_6-acetone the central peak was referenced to 29.84 ppm, where spectra were recorded in CD_3OD the central peak was referenced to δ 49.00 ppm.

Infrared Spectroscopy

Infrared spectra were recorded on a Shimadzu FT-IR 8400S spectrophotometer. Absorptions are reported in wavenumbers (ν_{max}, cm^{-1}). Samples were analysed as a thin film (from neat or evaporation from $CDCl_3$ or CH_2Cl_2) on NaCl plates or as a solid on a Perkin Elmer Spectrum 100 FT-IR spectrometer fitted with a diamond window universal ATR sampling accessory.

Gas Chromatography / Mass Spectrometry

Mass spectroscopy and Hi-Res mass spectrometry was performed on a Kratos Concept ISQ mass instrument using electron impact mass spectrometry or by LSIMS with *m*-nitrobenzoic acid as the matrix. Alternately a Thermoscientific I.T.Q. Orbitrap using either ESI or APCI modes was used. The molecular ion and mass fragments are quoted, with relative intensities of the peaks referenced to the most intense taken as 100%.

Sample mixtures were analysed using a Varian CP – 3800 Gas Chromatograph loaded with a Varian FactorFour: CC. VF – 5 ms, 0.25mm, 0.25 µm column. This fed directly into a Varian 1200 Triple Quadrapole mass spectrometer which recorded mass spectrum using electron impact mass spectrometry (EI).

Chemical

Reagents were used as received from their suppliers (unless otherwise stated). Anhydrous solvents (tetrahydrofuran, diethyl ether, and toluene) were dried using a Innovative Technology SPS400-7 solvent drying machine fitted with activated alumina and copper catalyst columns. Anhydrous dichloromethane was obtained by

distillation from calcium hydride. Dimethylsulphoxide (DMSO), dimethylformamide (DMF), and methanol were dried using fresh 4 Å molecular sieves for a minimum of 24 h before use.

Organic extracts were dried with anhydrous $MgSO_4$ unless otherwise stated.

Column Chromatography

Column chromatography was performed using column grade silica gel (32 – 63 μm) following the general method reported by Still with the solvent used giving a retention factor (R_f) of ~0.3 of the targeted compound.[164]

Thin Layer Chromatography (TLC)

Thin layer chromatography was conducted using Merck silica gel 60 F254 aluminium backed sheets. TLC plates were visualised under 254nm UV lamp and / or by treatment with an alkaline potassium permanganate dip (3g $KMnO_4$, 20g K_2CO_3, 5mL 5% aqueous NaOH, 300mL water) or a ceric (IV) phosphomolybdic acid dip, which contains phosphomolybdic acid (37.5g), ceric sulphate (7.5g), sulphuric acid (37.5 mL), and water (720 mL); then developed by heating with a heat gun.

Melting Points

Melting points were carried out on a micro melting point apparatus, Yanagimoto Seisakusho or Reichert, and are uncorrected.

X-Ray Crystallography - Cif files on the CD provided.

Single crystal x-ray structure determinations and structure solutions of compounds **60**, **62**, **93**, **220** and **224** were carried out by Dr. Roderick Jones in the School of Chemistry, University of Tasmania at -80°C using an Enraf-Nonius CAD4 diffractometer with a graphite single crystal monochromated molybdenum radiation source, with λ assumed to be 0.71073 Å (K_α). All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed in calculated positions and refined using a riding model with fixed C-H distances of 0.95 Å (sp^2C-H) and 0.98 Å (CH_3), and Uiso(H) = 1.2Ueq(C) (sp^2) and 1.5Ueq(C) (sp^3).

Compound **72** and **84** was carried out by Dr Jonathan White in the Bio21 Institute, School of Chemistry, University of Melbourne. X-ray structure determinations and structure solution were recorded on an Enraf-Nonius CAD4f diffractometer operating in the θ/2θ scan mode at low room temperature using Cu-Kα radiation source, with Nickel filtered, λ = 1.5418 Å. Data processing, absorption corrections,[165] structure solution,[166] and refinement[167] were implemented within WingX suite of programs.[168]

OR

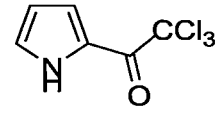
Intensity data were collected by Dr Jonathan White with a Bruker SMART Apex CCD detector using Mo-Kα radiation (graphite crystal monochromator λ = 0.71073 A). Data were reduced using the program SAINT. The temperature during data collection was maintained at 130.0(1) using an Oxford Cryostream cooling device. The structures were solved by direct methods and difference Fourier synthesis.

Thermal ellipsoid plots were generated using the program ORTEP-3integrated within the WINGXsuite of programs.

6.1 Experimental Procedures for Compounds Described in Chapter 1

6.1.1 Formation of 4-Aryl substituted pyrroles

2,2,2-Trichloro-1-(1*H*-pyrrol-2-yl)ethanone (48)



Trichloroacetyl chloride (28.8 g, 0.158 mol) was added drop-wise to a solution of pyrrole (**1**) (9.7 g, 0.144 mol) in diethyl ether (500 mL) under nitrogen at room temperature. The reaction mixture was stirred for 2 h, quenched with sodium carbonate and extracted with diethyl ether. The combined organic layers were then dried and removed under vacuum to give the product, a dark purple solid in 96% yield, which was used without further purification. The spectral data was shown consistent with literature.[51]

IR ν_{max} (cm^{-1}): 3318, 1655, 1535, 1136, 1112, 1063, 1035, 843, 755.

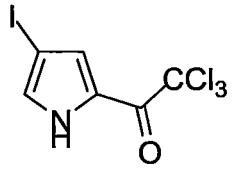
^{1}H NMR δ: 6.38 (dt, *J* = 4.1, 2.5 Hz, 1H), 7.15 – 7.18 (m, 1H), 7.37 – 7.40 (ddd, *J* = 3.9, 2.5, 1.3 Hz, 1H), 9.51 (s, 1H).

^{13}C NMR δ: 96.4, 110.9, 121.2, 125.4, 132.3, 170.8.

GENERAL PROCEDURE FOR IODINATION

Iodine was added to a mixture of pyrrole and silver trifluoroacetate in chloroform at 0°C under a nitrogen atmosphere and the mixture stirred at room temperature for 16 h with the exclusion of light. The reaction was quenched with aqueous sodium sulfite and brine, and extracted with dichloromethane. The combined organic extracts were dried and filtered through a thin layer of silica gel. The solution was concentrated under reduced pressure to give the desired product.

2,2,2-Trichloro-1-(4-iodo-1*H*-pyrrol-2-yl)ethanone (56)

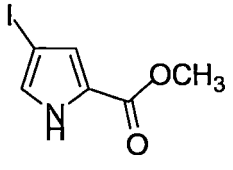


The general procedure of iodination was followed using 2,2,2-trichloro-1-(1H-pyrrol-2-yl)ethanone **48** (3.0 g, 14 mmol), silver trifluoroacetate (3.7 g, 17 mmol) and iodine (3.9 g, 16 mmol) in chloroform (50 mL). Iodo-ketone **56** was obtained as an off-white solid in 86% yield, and spectral data was consistent with that previously reported.[53]

1H NMR δ: 7.20 (dd, *J* = 3.1, 1.3 Hz, 1H), 7.45 (dd, *J* = 2.6, 1.3 Hz, 1H), 9.63 (s, 1H)

HALOFORM REACTION

Methyl-4-iodo-1*H*-pyrrole-2-carboxylate (58)



A mixture of iodopyrrole ketone **52** (0.47 g, 1.94 mmol) and potassium carbonate (0.13 g, 0.97 mmol) in methanol (25 mL) was stirred at room temperature for 15 h with the exclusion of light. The reaction was quenched by the addition of water and aqueous sodium bicarbonate, and extracted with dichloromethane and dried. The solvent was filtered through a thin layer of silica gel, eluting with dichloromethane and reduced under pressure to give the title compound as an off-white powder in 88% yield.

Melting point: 98-102 °C

IR ν_{max} (cm^{-1}): 3283, 2360, 1689, 1376, 1313, 1204, 1117, 1130, 909, 761.

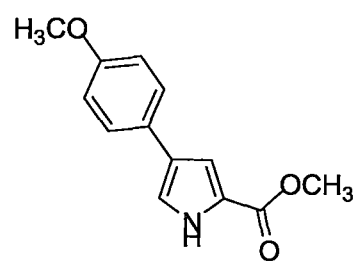
1H NMR δ: 3.86 (s, 3H), 6.98 (dd, *J* = 2.7, 1.5, 1H), 7.01 (dd, *J* = 2.9, 1.5 Hz, 1H), 9.53 (s, 1H).

^{13}C NMR δ: 50.9, 109.4, 114.3, 121.4, 122.2, 159.3

GENERAL PROCEDURE FOR LIGANDLESS SUZUKI-MIYAURA CROSS-COUPLING

A mixture of iodopyrrole and boronic acid in acetone and aqueous potassium carbonate (2 M) was subjected to three freeze thaw cycles to remove dissolved oxygen. Palladium acetate was added and the mixture heated for 1 h. A further addition of arylboronic acid and palladium acetate was added and heating continued until completion was monitored by TLC. The mixture was cooled to room temperature, washed with water, sodium bicarbonate (2 M) and brine, and extracted with dichloromethane. The organic layer was dried and evaporated to give the desired product after purification by column chromatography.

Methyl 4-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (60)



The general procedure for ligandless Suzuki-Miyaura cross-coupling was followed, using iodopyrrole methyl ester **58** (250 mg, 0.99 mmol), *p*-methoxy phenylboronic pincol ester (270 mg, 1.15 mmol), palladium acetate (20 mg, 0.09 mmol), acetone (10 mL) and aqueous potassium carbonate (2 M, 10 mL). After heating for 4 h, a

further portion of boronic acid (100 mg, 0.42 mmol) and palladium acetate (20 mg, 0.09 mmol) were added and heated for a further 4 h. The title compound was obtained after purification by column chromatography (30% ethyl acetate / hexane as eluent) in 52% yield. Recrysallisation from dichloromethane / hexane gave pale yellow crystals.

Melting point: 183 – 189 °C

MS: Found: M^+, 231.0898. $C_{12}H_{11}NO_2$ requires M^+, 231.0895.

m/z (EI): 231 (50%, M^+), 199 (100), 184 (50), 156 (25), 128 (20), 101 (15).

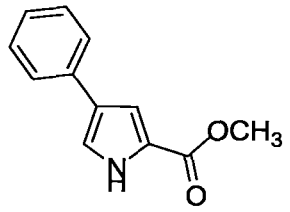
IR ν_{max} (cm^{-1}): 3836, 1680.

^{1}H NMR δ: 3.82 (s, 3H), 3.88 (s, 3H), 6.89 (m, 2H), 7.14 (dd, *J* = 3.0, 1.5 Hz, 1H), 7.15 (dd, *J* = 3.0, 1.5 Hz, 1H), 7.43 (m, 2H), 9.15 (bs, 1H).

^{13}C NMR δ: 51.5, 55.3, 112.3, 114.2, 118.8, 126.4, 128.5, 129.4, 135.6, 159.2, 160.9.

Crystal data: $C_{13}H_{13}NO_3$, *M* = 231.25, monoclinic, space group $P2_1/c$, *a* = 7.6597(14), *b* = 5.584(5), *c* = 26.937(5)Å, α = 90, β = 96.899(16), γ = 90°, *V* = 1143.8(10)Å^3, *Z* = 4, *D*c = 1.343 g cm^{-3}, specimen: colourless block, 0.46 x 0.44 x 0.32 mm, 2589 measured reflections, *R*int = 0.026, *R* = 0.0369 for 1691 'observed' data ((*I*) >2σ(*I*)), *wR* = 0.097, and GOOF = 1.056 for all data '1997'.

Methyl 4-phenyl-1*H*-pyrrole-2-carboxylate (61)



The general procedure for ligandless Suzuki-Miyaura cross-coupling was followed using iodopyrrole **58** (375 mg, 1.50 mmol), phenylboronic acid (211 mg, 1.73 mmol), palladium acetate (20 mg, 0.09 mmol), acetone (10 mL) and aqueous potassium carbonate (5 mL). Further arylboronic acid (110 mg, 0.90 mmol) and palladium acetate (20 mg, 0.09 mmol) were added after 2 h, and heated for a further 4 h. The product was purified by column chromatography (50% ethyl acetate / hexanes as eluent) to give the title compound as an off-white solid in 83% yield.[58]

Melting Point: 176 – 180 °C (lit.[58] mp. 197 – 198 °C)

MS: Found: M^+, 201.0789. $C_{12}H_{11}NO_2$ requires M^+, 201.0809.

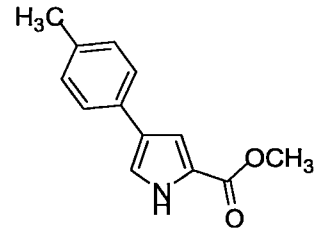
m/z (EI): 201 (50%, M^+), 169 (100), 141 (50), 140 (40), 115 (30), 114 (30).

IR ν_{max} (cm^{-1}): 3416, 1677, 1602, 1461, 1348, 1306, 1216, 1132, 756, 722, 703.

^{1}H NMR δ: 3.89 (s, 3H), 7.19 – 7.25 (m, 3H), 7.33 – 7.38 (m, 2H), 7.50 – 7.54 (m, 2H), 9.32 (s, 1H).

^{13}C NMR δ: 51.4, 112.7, 119.6, 125.4, 127.1, 129.6, 131.8, 136.2, 138.4, 162.2.

Methyl 4-*p*-tolyl-1*H*-pyrrole-2-carboxylate (62)



The general procedure for the ligandless Suzuki-Miyaura cross-coupling was followed using iodopyrrole **58** (251 mg, 1.00 mmol), *p*-tolylboronic acid (148 mg, 1.08 mmol), palladium acetate (20 mg, 0.09 mmol), acetone (10 mL) and 2M aqueous potassium carbonate (5 mL). Further *p*-tolylboronic acid (75.7 mg, 0.55 mmol) and palladium acetate (20 mg) were added after 2 h and heating continued for a further 4 h. The product was purified by column chromatography (20% ethyl acetate / hexanes as eluent) to give the title compound as an off-white solid in 64% yield. Suitable crystals for X-ray analysis were grown from dichloromethane / hexane.

Melting point: 176 – 180 °C

MS: Found: M^+, 215.0992. $C_{13}H_{13}NO_2$ requires M^+, 215.0995.

m/z (EI): 215 (40%, M^+), 154 (100), 139 (20), 80 (40).

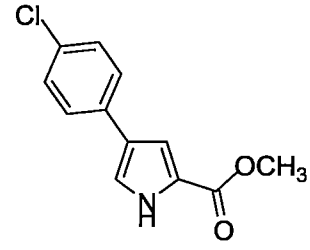
^{1}H NMR δ: 2.35 (s, 3H), 3.89 (s, 3H), 7.16 – 7.19 (m, 3H), 7.21 (dd, *J* = 3.0, 1.5, 1H), 7.40 – 7.44 (m, 1H), 9.32 (bs, 1H)

^{13}C NMR δ: 21.3, 51.4, 112.7, 119.6, 125.4, 127.1, 129.6, 131.8, 136.2, 138.4, 162.2.

Crystal Data: $C_{13}H_{13}NO_2$, M_r = 215.24, monoclinic, *P* 2_1 */n*, *a* = 7.7119 (15) Å, *b* = 5.4554 (11) Å, *c* = 26.385 (5) Å, β = 94.61 (3)°, *V* = 1106.5 (4) Å^3, *Z* = 4, D_x = 1.292 Mg m^{-3}, Mo *Kα* radiation, μ = 0.09 mm^{-1}, Block,

colourless, 0.55 × 0.55 × 0.45 mm, 1975 measured reflections, 1931 independent reflections, 1648 reflections with $I > 2\sigma(I)$, $R_{int} = 0.020$, $\theta_{max} = 25.0°$, $wR = 0.135$, and GOOF = 1.08 for all data '1931'.

Methyl 4-(4-chlorophenyl)-1*H*-pyrrole-2-carboxylate (63)



The general procedure for the ligandless Suzuki-Miyaura cross-coupling was followed heating iodopyrrole **58** (251 mg, 1.00 mmol), *p*-chloro-phenylboronic acid (262 mg, 1.10 mmol), palladium acetate (20 mg, 0.09 mmol), acetone (10 mL) and 2M aqueous potassium carbonate (5 mL). *p*-Chlorophenyl- boronic acid (147 mg, 0.0.62 mmol) and palladium acetate (20 mg, 0.09 mmol) and added after 1 h. Heating continued for a further 4 h. The title compound was obtained in 55% after purification by column chromatography (20% ethyl acetate / hexanes of eluent).

^{1}H NMR δ: 3.88 (s, 3H), 7.15 (m, 1H), 7.21 (m, 1H), 7.32 (m, 2H), 7.43 (m, 2H), 9.62 (bs, 1H)

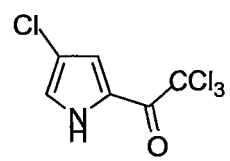
^{13}C NMR δ: 51.5, 106.9, 120.7, 122.6, 128.9, 129.4, 134.3, 134.5, 135.6, 159.9.

6.1.2 Formation of C5 substituted pyrroles

GENERAL PROCEDURE FOR CHLORINATION (ADOPTED FROM THE METHOD OF BELANGER'S)[44]

To a solution of pyrrole in chloroform, sulfuryl chloride was added slowly at 0^0C. The mixture was stirred at room temperature with the exclusion of light until completion as indicated by TLC. The solution was washed with sodium carbonate (2 M) and extracted the aqueous phase with dichloromethane. The combined organic extracts were dried and the solvent reduced by rotary evaporation to yield the desired compound.

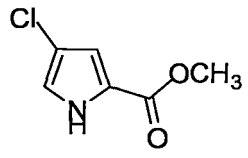
2,2,2-Trichloro-1-(4-chloro-1*H*-pyrrol-2-yl) ethanone (64)



The general procedure for chlorination was followed using trichloro acetylpyrrole **48** (500 mg, 4.0 mmol) and sulfuryl chloride (320 mg, 4.1 mmol) in chloroform (25 mL). The crude product was purified by passing through a plug of silica gel eluting with dichloromethane. The product identified was as an off-white solid in 83% yield and used in the next step without further purification.

^{1}H NMR δ: 7.11 (dd, *J* = 3.3, 1.5 Hz, 1H), 7.27 (dd, *J* = 2.7, 1.5 Hz, 1H), 9.42 (bs, 1H)

Methyl 4-chloro-1*H*-pyrrole-2-carboxylate (65)

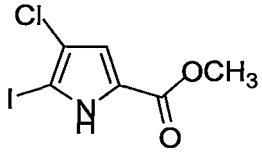


Trichlroracetyl pyrrole **64** (479.1 mg, 1.956 mmol) was stirred in a mixture of methanol (25 mL) and potassium carbonate (250 mg, 1.80 mmol) for 15 h. Water (20 mL) was added to the mixture and extracted with dichloromethane. The organic extract was dried and evaporated to give the crude product, which was filtered through a plug of silica gel eluting with dichloromethane to give the title compound (88%) as an off-white crystal. The compound was used without further purification.

^{1}H NMR δ: 3.83 (s, 3H), 6.80 (dd, *J* = 2.4, 1.8 Hz, 1H), 6.89 (dd, *J* = 3.0, 1.5 Hz, 1H), 9.90 (bs, 1H).

^{13}C NMR δ: 51.6, 109.4, 114.8, 121.6, 122.9, 159.8.

Methyl 4-chloro-5-iodo-1*H*-pyrrole-2-carboxylate (42)



Iodination was followed as described in the general procedure using methyl 4-chloropyrrole-2-carboxylate (1.0 g, 6.3 mmol), silver trifluoroacetate (1.4 g, 6.3 mmol) and iodine (0.88 g, 6.9 mmol) in chloroform (30 mL). The title compound was obtained in 86% yield as a yellow-white solid, and used without further purification.

Melting Point: 123-128 °C

MS: Found: M^+, 284.9053. $C_6H_5{}^{35}ClINO_2$ requires M^+, 284.9583.

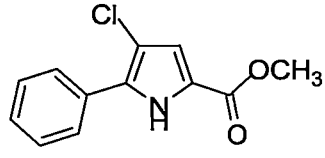
m/z (EI): 287 (30%,M^+, $C_6H_5NO_2{}^{37}ClI$), 285 (80%, M^+, $C_6H_5{}^{35}ClINO_2$), 255 (40), 253 (90), 181 (35), 169 (30), 131 (40), 119 (35), 69 (100).

IR ν_{max} (cm^{-1}): 3249, 1692, 1546, 1439, 1392, 1331, 1237, 1209, 998, 983.

^{1}H NMR δ: 3.91 (s, 3H), 6.80 (d, *J* = 2.7 Hz), 10.19 (bs, 1H).

^{13}C NMR δ: 52.1, 109.4, 114.4, 121.8, 122.4, 159.3.

Methyl 4-chloro-5-phenyl-1*H*-pyrrole-2-carboxylate (66)

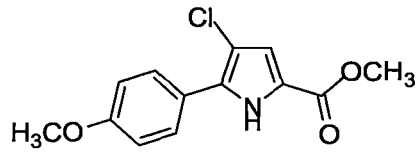


The general procedure described for the ligandless Suzuki-Miyaura cross-coupling was used with iodopyrrole **42** (131 mg, 0.461 mmol), phenylboronic acid (72.3 mg, 0.592 mmol), palladium acetate (20 mg, 0.09mmol), acetone (10 mL) and 2M aqueous potassium carbonate (5 mL). Phenylboronic acid (16.5 mg, 0.135 mmol) and palladium acetate (20 mg, 0.09 mmol) were added after 2 h and the mixture heated for a further 4 h. The title compound was obtained in 75% yield as an off-white solid after column chromatography (20% ethyl acetate / hexanes as eluent). The spectral data for **66** was consistent with that reported in literature.[67]

^{1}H NMR δ: 3.84 (s, 3H), 6.91 (d, J = 3.0 Hz, 1H), 7.40 (m, 3H), 7.72 (m, 2H), 9.82 (bs, 1H).

^{13}C NMR δ: 51.5, 110.7, 114.5, 121.9, 123.7, 127.7, 128.3, 128.4, 133.6, 159.4.

Methyl 4-chloro-5-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (67)



The general procedure of ligandless Suzuki-Miyaura cross-coupling was employed with iodopyrrole **42** (370.0 mg, 1.298 mmol), *p*-methoxyphenyl boronic acid (670.7 mg, 2.865 mmol), palladium acetate (20 mg, 0.09 mmol), acetone (20 mL) and 2M aqueous potassium carbonate (10 mL). Further aryl boronic acid (367.5 mg, 1.569 mmol) and palladium acetate (20 mg, 0.09 mmol) were added after 1 h, and heating continued for a further 5 h. The crude product was purified by column chromatography (30% ethyl acetate-hexanes as eluent) to give the title compound as a white solid in 82% yield.

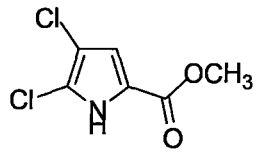
m/z (EI): 265 (68%, M^+, $C_{13}H_{12}{}^{37}ClNO_3$), 267 (25%, M^+, $C_{13}H_{12}{}^{35}ClNO_3$), 233 (85), 235 (25), 170 (100).

^{1}H NMR δ: 3.85 (s, 6H), 6.88 (d, *J* = 2.8 Hz, 1H), 6.94 - 7.03 (m, 2H), 7.58 – 7.67 (m, 2H), 9.23 (bs, 1H).

^{13}C NMR δ: 51.94, 55.51, 114.42 (x2), 116.53, 120.54, 122.52, 128.42 (x2), 159.80, 161.25.

6.1.3 Formation of C5-substituted pyrroles

Methyl 4,5-dichloro-1*H*-pyrrole-2-carboxylate (69)



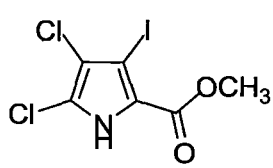
The general procedure for chlorination was followed using pyrrole ester **44** (0.50 g. 4.0 mmol) and sulfuryl chloride (1.08 g, 7.9 mmol) in chloroform (50 mL). The crude product was obtained after passing through a thin layer of silica gel eluting with dichloromethane to give the product **69** as an off-white solid in 91% yield, and was used without further purification. No spectral data has been reported previously for this known compound.[169]

Melting point: 168 – 170 °C (lit.[169] mp 164 – 165.5 °C)

^{1}H NMR δ: 3.87 (s, 3H), 6.81 (d, *J* = 3.0 Hz), 9.51 (bs, 1H)

^{13}C NMR δ: 55.4, 109.4, 116.4, 124.4, 131.6, 171.8.

Methyl 4,5-dichloro-3-iodo-1*H*-pyrrole-2-carboxylate (70)



The general procedure for iodination was followed starting with pyrrole ester **69** (0.76 g, 3.9 mmol), silver trifluoroacetate (0.86 g, 4.3 mmol) and iodine (1.1 g, 4.3 mmol) in chloroform (20 mL). After passing through a thin layer of silica gel eluting with dichloromethane, **70** was obtained as a brown solid in 77% yield.

Melting Point: 188 – 195 °C

MS: Found: M^+, 318.8661. $C_6H_4{}^{35}Cl_2INO_2$ requires M^+, 318.8663.

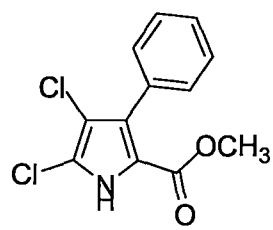
m/z (EI): 323 (10%, M^+, $C_6H_4{}^{37}Cl_2INO_2$), 321 (45%, M^+, $C_6H_4{}^{35}Cl{}^{37}ClINO_2$), 319 (60%, M^+, $C_6H_4{}^{35}Cl_2INO_2$), 289 (60), 287 (100), 277 (20), 275 (20), 235 (15), 233 (20).

IR ν_{max} (cm^{-1}): 3199, 1689, 1672, 1438, 1309, 1249, 1204, 944.

^1H NMR δ: 3.92 (s, 3H), 9.72 (bs, 1H).

^{13}C NMR δ: 52.3, 72.9, 76.6, 122.0, 123.4, 159.3.

Methyl 4,5-dichloro-3-phenyl-1*H*-pyrrole-2-carboxylate (71)



The general procedure for ligandless Suzuki-Miyaura cross-coupling was followed, using iodopyrrole **70** (62 mg, 0.82 mmol), phenylboronic acid (110 mg, 0.09 mmol), palladium acetate (20 mg, 0.09 mmol), acetone (20 mL) and 2M aqueous potassium carbonate (10 mL). Further phenylboronic acid (100 mg, 0.82 mmol) and palladium acetate (20 mg, 0.09 mmol) were added after 1 h, and heating continued for a further 5 h. The product was purified by column chromatography (10% ethyl acetate / hexanes as eluent) to give the title compound as a light-yellow solid in 94% yield.

Melting point: 129-131°C

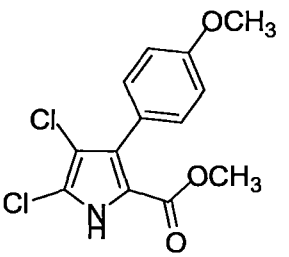
m/z (EI): 273 (15%, M^+, $C_{12}H_9{}^{37}Cl_2NO_2$), 271 (50%, M^+, $C_{12}H_9{}^{35}Cl{}^{37}ClNO_2$), 269 (75%, M+, $C_{12}H_9{}^{35}Cl_2NO_2$), 239 (75), 237(100), 176 (30), 174 (75).

IR ν_{max} (cm^{-1}): 3235, 2952, 1677, 1606, 1559, 1507, 1443, 1403, 1323, 1266, 1196, 1159.

^{1}H NMR δ: 3.73 (s, 3H), 7.39 – 7.61 (m, 5H), 9.89 (bs, 1H).

^{13}C NMR δ: 50.9, 106.2, 116.8, 124.4, 126.9, 128.7, 129.4, 131.5, 136.4, 159.7.

Methyl 4,5-dichloro-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (72)



The general procedure for the ligandless Suzuki-Miyaura cross-coupling was employed, using iodopyrrole **70** (231 mg, 0.72 mmol), *p*-methoxyphenyl boronic acid (190 mg, 1.12 mmol), palladium acetate (20 mg), acetone (20 mL) and 2M aqueous potassium carbonate (10 mL). Further aryl boronic acid (97.1 mg, 0.64 mmol) and palladium acetate (20 mg, 0.09 mmol) were added after 1 h, and heating continued for a further 5 h. The product was purified by column chromatography (10% ethyl acetate / hexanes as eluent) to give **67** as a yellow crystalline solid in 78% yield.

m/z (EI): 301 (50%, M^{+}, $C_{13}H_{11}{}^{37}Cl_2NO_3$), 299 (50%, M+, $C_{13}H_{11}{}^{35}Cl_2NO_3$), 269 (65), 267 (100), 206 (35), 204 (100).

^{1}H NMR δ: 3.73 (s, 3H), 3.85 (s, 3H), 6.95 (m, 2H), 7.35 (m, 2H), 9.62 (bs, 1H).

^{13}C NMR δ: 52.16, 55.57, 113.53, 114.61, 114.87, 117.01, 123.89, 128.92, 131.88, 132.06, 159.64.

Crystal data: $C_{13}H_{11}Cl_2NO_3$, *M* = 300.13, monoclinic, space group $P2_1/n$, *a* = 12.198(2), *b* = 12.5270(10), *c* = 17.940(3)Å, α =90, β = 99.040(10), γ = 90°, *V* = 2707.3(7)Å^3, *Z* = 8, *D*c = 1.473 g cm^{-3}, specimen: colourless

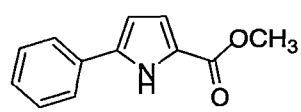
block, 0.5 x 0.2 x 0.2 mm, 5440 measured reflections, *R*int = 0.066, *R* = 0.026 for 3751 'observed' data ((*I*) >2σ(*I*)), *wR* = 0.113, and GOOF = 1.020 for all data '5132'.

6.1.4 Reductive Dechlorination

GENERAL PROCEDURE FOR CATALYTIC HYDROGENATION

A mixture of pyrrole in methanol or ethanol containing a hydrogenation catalyst in a hydrogenation vessel was shaking under an atmosphere of hydrogen at 40 psi on a Parr shaker hydrogenator until no further reduction in pressure was observed. The catalysts were removed by filtrating through Celite and the solvent removed by rotary evaporation to give the crude reaction product.

Methyl 5-phenyl-1*H*-pyrrole-2-carboxylate (73)



Catalytic hydrogenation was performed under the standard procedure using chloropyrrole **66** (40 mg, 0.17 mmol) and 10% w/w palladium on carbon (20 mg) in methanol (5 mL). The crude product was obtained after 6 h. After column chromatography (20% ethyl acetate / hexanes as eluent), the product was obtained as a white solid in 82% yield. The spectral data was consistent with that reported in literature.[67]

MS: Found: M^+, 201.0789. $C_{12}H_{11}NO_2$ requires M^+, 201.0687.

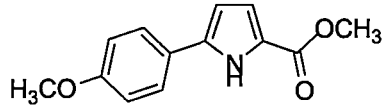
m/z (EI): 201 (90%,M^+), 169 (100), 141 (70), 140 (45), 115 (45), 114 (30).

IR ν_{max} (cm^{-1}): 3319, 2951, 1686, 1510, 1468, 1441, 1405, 1269, 1195, 1006, 758.

^{1}H NMR δ: 3.88 (s, 3H), 6.54 (dd, *J* = 3.9, 2.7 Hz, 1H), 6.96 (dd, *J* = 3.9, 2.4 Hz, 1H), 7.31 (m, 1H), 7.41 (m, 2H), 7.60 (m, 2H), 9.52 (bs, 1H).

^{13}C NMR δ: 51.8, 108.3, 115.3, 117.1, 121.5, 128.0, 129.2, 131.5, 131.7, 134.5, 161.9.

Methyl 5-(*4*-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (74)

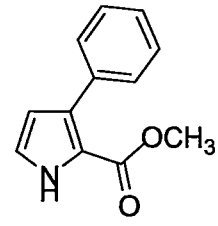


The general procedure for catalytic hydrogenation was followed using chloropyrrole **67** (11.4 mg, 0.043 mmol) and 10% w/w palladium on carbon (10 mg) in methanol (5 mL). The crude product was obtained after 6 h. The title compound was isolated as a colourless crystalline solid in 37% after purification with a column chromatography (20% ethyl acetate/hexanes as eluent). The spectral data showed consistent to that reported in literature.[67]

^{1}H NMR δ: 3.84 (s, 3H), 3.87 (s, 3H), 6.42 – 6.44 (dd, *J* = 3.0, 2.7 Hz, 1H), 6.92 – 6.97 (m, 3H), 7.47 – 7.52 (m, 2H), 9.22 (bs, 1H).

^{13}C NMR δ: 53.5, 56.9, 110.4, 114.6, 120.1, 122.3 128.1, 128.5, 134.8, 159.2, 160.6.

Methyl 3-phenyl-1*H*-pyrrole-2-carboxylate (75)



The general procedure for catalytic hydrogenation was followed staring with dichloropyrrole **71** (83.0 mg, 0.307 mmol) and 10% w/w palladium on carbon (10 mg) in methanol (5 mL). The title product was obtained in 87% yield as a yellow oil after column chromatography (30% ethyl acetate / hexanes as eluent).

MS: Found: M^+, 201.0792. $C_{12}H_{11}NO_2$ requires M^+, 201.0789.

m/z (EI): 201 (80%, M^+), 169 (100), 141 (35), 140 (50), 115 (40), 114 (25).

IR ν_{max} (cm^{-1}): 3321, 1685, 1557, 1503, 1440, 1398, 1283, 1203, 1143, 896, 788.

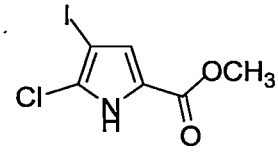
^{1}H NMR δ: 3.78 (s, 3H), 6.36 (m, 1H), 6.96 (m, 1H), 7.35 (m, 3H), 7.56 (m, 2H), 9.25 (bs, 1H).

^{13}C NMR δ: 51.6, 112.8, 118.0, 122.2, 127.2, 127.9, 129.6, 132.5, 135.3, 161.9.

6.2 Experimental Procedures for Compounds Described in Chapter 2

6.2.1 Formation of Lamellarin Q Dimethyl Ether

Methyl 5-chloro-4-iodo-1*H*-pyrrole-2-carboxylate (77)



The general procedure for chlorination was used starting with iodopyrrole **58** (1.00 g, 4.3 mmol) and sulfuryl chloride (0.59 g, 4.4 mmol) in chloroform (15 mL).

The crude product was obtained as a pale-yellow solid in 84% yield, which was used without further purification.

Melting Point: 154 – 156 °C

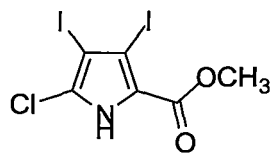
MS: Found: $M^{+\bullet}$, 284.9055. $C_6H_5{}^{35}ClINO_2$ requires $M^{+\bullet}$, 284.9583.

m/z (EI): 287 (45%, M^+, $C_6H_5{}^{37}ClINO_2$) 285 (70%, M^+, $C_6H_5{}^{35}ClINO_2$) 255 (30), 253 (100), 266 (10), 161 (15), 127 (20), 98 (30).

IR ν_{max} (cm^{-1}): 3222, 1700, 1542, 1435, 1395, 1239, 1206, 759.

^1H NMR δ: 3.86 (s, 3H), 6.94 (d, J = 2.7 Hz, 1H), 9.52 (bs, 1H).

Methyl 5-chloro-3,4-diiodo-1*H*-pyrrole-2-carboxylate (78)



The title compound was obtained using the general procedure of iodination using pyrrole ester **77** (509 mg, 1.79 mmol), iodine (497 mg, 1.27 mmol), and silver trifluoroacetic acid (497 mg, 2.26 mmol) in chloroform (50 mL). The crude product was purified by passing through a thin layer of silica gel eluting with ethyl acetate to obtain **78** as a pale yellow solid in 89% yield. The compound was used in further manipulation without further purification.

Melting Point: 200 – 204 °C

MS: Found: $M^{+\bullet}$, 410.8022. $C_6H_4{}^{35}ClI_2NO_2$ requires $M^{+\bullet}$, 410.8020.

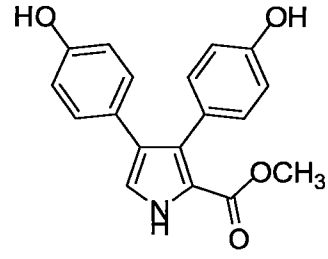
m/z (EI): 413 (30%, M^+, $C_6H_4NO_2{}^{37}ClI_2$) 411 (85%, M^+, $C_6H_4{}^{35}ClI_2NO_2$), 381 (35), 379 (100), 345 (15), 319 (15), 287 (30), 253 (20), 224 (25), 163 (10), 127 (10).

IR ν_{max} (cm^{-1}): 3204, 1678, 1559, 1446, 1379, 1283, 1242, 764, 720.

^{1}H NMR δ: 3.91 (s, 3H), 9.63 (s, 1H).

Methyl 3,4-bis(4-hydroxyphenyl)-1*H*-pyrrole-2-carboxylate (80)

(Lamellarin Q)

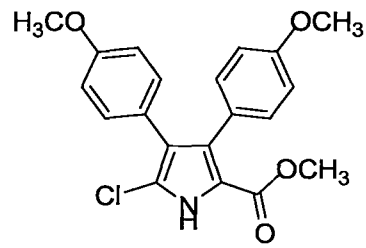


The title compound was obtained using the following two-step reaction.

Firstly, the general procedure of ligandless Suzuki-Miyaura cross-coupling was followed starting with pyrrole **78** (103 mg, 0.25 mmol), *p*-hydroxyphenyl boronic acid (77.5 mg, 0.56 mmol), palladium acetate (20 mg, 0.09 mmol) in a mixture of acetone (10 mL) and 2M aqueous potassium carbonate (5 mL). After heating for 3 h, portions of arylboronic acid (40.0 mg, 0.28 mmol) and palladium acetate (20 mg) were added and the mixture heated for a further 4 h. The crude product was then subjected to the general catalytic hydrogenation procedure with 10% w/w palladium on carbon (20 mg) in methanol (10 mL) for 6 h. The title compound was obtained in 6% yield after purification by column chromatography (50% ethyl acetate / hexanes as eluent). The spectral data was shown consistent with that reported in literature.[74]

^{1}H NMR δ (Acetone d_6): 3.64 (s, 3H), 6.75 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H) 7.07 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 3.2 Hz, 1H), 8.35 (bs, 2H), 10.21 (bs, 1H).

Methyl 5-chloro-3,4-bis(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (84)



The general procedure for the ligandless cross-coupling was followed starting with iodopyrrole **78** (254 mg, 0.62 mmol), *p*-methoxyphenyl boronate pincol ester (318 mg, 1.36 mmol) and palladium acetate (20 mg, 0.09 mmol) in a mixture of acetone (10 mL) and 2M aqueous potassium carbonate (5 mL). An additional of boronate ester (135 mg, 0.62 mmol) and palladium acetate (20 mg, 0.09 mmol) were added after 2 h, and the mixture heated for a further 5 h. The product was obtained after column chromatography (20% ethyl acetate / hexanes as eluent) and recrystallised from dichloromethane / hexanes to yield **84** as a yellow crystalline solid in 45% yield.

Melting point: 168 –171 °C

MS: Found: M^+, 371.0924. $C_{20}H_{18}ClNO_4$ requires M^+, 371.0914.

m/z (EI): 373 (10%,M^+, $C_{20}H_{18}{}^{37}ClNO_4$), 371 (30%, M^+, $C_{20}H_{18}{}^{35}ClNO_4$), 341 (30), 339 (100), 324 (10), 276 (50), 261 (15), 233 (10), 190 (15).

IR ν_{max} (cm^{-1}): 3252, 2952, 2836, 1673, 1613, 1537, 1440, 1391, 1246.

^{1}H NMR δ: 3.74 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 6.78 (m, 4H), 7.04 (m, 2H), 7.11 (m, 2H), 9.71 (s, 1H).

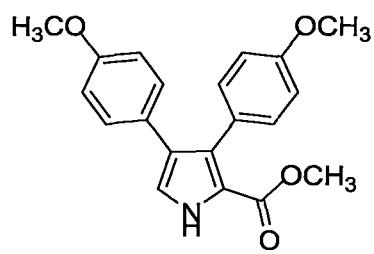
^{13}C NMR δ: 51.62, 55.25, 55.26, 113.12, 113.63, 114.56, 117.35, 122.69, 124.53, 125.55, 130.53, 131.23, 131.95, 158.44, 158.77, 160.78.

Anal. Calcd. for $C_{20}H_{18}ClNO_4$: C, 64.61; H, 4.88; Cl, 9.54; N, 3.77. Found: C, 64.45; H, 4.91; N, 3.87.

Crystal data: $C_{20}H_{18}ClNO_4$, M = 371.8, triclinic, space group P-1, a = 10.7431(8), b = 13.5397(10), c = 19.3750(15)Å, α = 101.138(2), β = 97.455(2), γ = 96.572(2)°, V = 2713.5(4)Å^3, Z = 6, Dc = 1.365 g cm^{-3}, specimen: colourless block, 0.15 x 0.15 x 0.15 mm, 14434 measured reflections, Rint = 0.051, R = 0.0623 for 3608 'observed' data ((I) >2σ(I)), wR = 0.061, and GOOF = 0.591 for all data '9442'.

Methyl 3,4-bis(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (22)

(Lamellarin Q dimethyl ether)



The general procedure for the catalytic hydrogenation was followed starting with chloropyrrole **84** (10 mg, 0.027 mmol) and 10% w/w palladium on carbon (20 mg) in methanol (5mL). After hydrogenating for 6 h, the title compound was obtained as a colourless crystal (72%) after purification by column chromatography (50% ethyl acetate / hexanes as eluent). The spectral data was consistent with that reported in literature.[1]

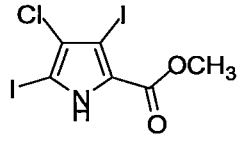
IR ν_{max} (cm^{-1}): 3343, 1691, 1611, 1536, 1438, 1377, 1290, 1245, 1177, 1034, 834.

^{1}H NMR δ: 3.73 (s, 3H), 3.76 (s, 3H), 3.82 (s, 3H), 6.75 (m, 2H), 6.84 (m, 2H), 7.03 (m, 3H), 7.19 (m, 2H), 9.23 (s, 1H).

^{13}C NMR δ: 51.6, 55.4, 55.5, 113.4, 113.8, 119.3, 120.1, 126.4, 127.1, 129.4, 131.8, 132.2, 141.2, 158.0, 158.5, 161.6.

6.2.2 Formation of 3,5-diaryl pyrroles

Methyl 4-chloro-3,5-diiodo-1*H*-pyrrole-2-carboxylate (92)



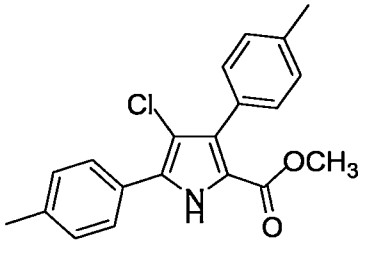
The title compound was obtained using general iodination procedure. Iodine (2.221 g, 11.05 mmol) was added to a mixture of chloro-pyrrole **65** (799.7 mg, 5.03 mmol) and silver trifluoroacetate (2.46 g, 11.2 mmol) in chloroform (50 mL) at 0^{O}C under nitrogen atmosphere. The title compound **92** was obtained as a pale yellow solid in 68% yield and used without further purification.

Melting point: 192 – 197 ^{O}C

IR ν_{max} (cm^{-1}): 3242, 1681, 1445, 1381, 1238.

^{1}H NMR δ: 3.92 (s, 3H), 9.96 (bs, 1H).

Methyl 4-chloro-3,5-di-*p*-tolyl-1*H*-pyrrole-2-carboxylate (93)



The general procedure for ligandless cross-coupling was followed using chloro-iodo pyrrole **93** (216.1 mg, 0.525 mmol), *p*-tolylboronic acid (175.6 mg, 1.29 mmol), palladium acetate (20 mg, 0.09 mmol), acetone (10 mL) and in 2M aqueous potassium bicarbonate solution (5 mL) and heated for 1 h. *p*-Tolylboronic acid

(175.6 mg, 1.29 mmol) and palladium acetate (20 mg, 0.09 mmol) were added and the mixture heated continuously for a further 12 h. The product was purified by column chromatography (20% ethyl acetate / hexane as eluent) to give the title compound in 78% yield. Recrystallisation from dichloromethane / hexane gave **93** as a yellow crystal suitable for X-ray crystallography.

Melting Point: 179 – 185 ^{O}C

MS: Found: M^+, 339.0786. $C_{20}H_{18}ClNO_2$ requires M^+, 339.0820.

m/z (EI): 341 (20%, M^+, $C_{20}H_{18}{}^{37}ClNO_2$), 339 (55%, M+, $C_{20}H_{18}{}^{35}ClNO_2$), 309 (20), 307 (60), 245 (20), 244 (100).

IR ν_{max} (cm^{-1}): 3288, 1676, 1450, 1292.

^{1}H NMR δ: 2.34 (s, 3H), 2.41 (s, 3H), 3.73 (s, 3H), 7.30 (m, 6H), 7.64 (d, *J* = 8.2 Hz, 2H), 9.19 (s, 1H).

^{13}C NMR δ: 21.69, 21.74, 51.90, 117.74, 127.26, 127.31, 128.37, 128.74, 129.37, 129.77, 130.47, 130.82, 131.74, 137.68, 138.92, 161.47.

Crystal data: $C_{20.5}H_{19}Cl_2NO_2$, *M* = 382.27, triclinic, space group *P*-1, *a* = 8.4547(17), *b* = 9.896(2), *c* = 12.314(3)Å, α =71.63(3), β = 82.93(3), γ = 74.28(3)°, *V* = 940.4(3)Å^3, *Z* = 2, *D*c = 1.350 g cm^{-3}, specimen: colourless plate, 0.38 x 0.36 x 0.36 mm, 3482 measured reflections, *R*int = 0.051, *R* = 0.049 for 2791 'observed' data ((*I*) >2σ(*I*)), *wR* = 0.146, and GOOF = 1.050 for all data '3314'.

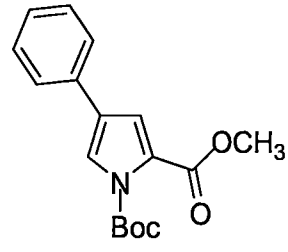
6.3 Experimental Procedures for Compounds Described in Chapter 3

6.3.1 Formation of 4-cis-Aryl-Proline Analogues

GENERAL PROCEDURE FOR *N*-BOC PROTECTION

The formation of *N*-Boc derivatives was performed by the standard conditions reported by Gilchrist.[84] Di-*tert*-butyl dicarbonate (Boc_2O) (1.1 equiv.) was added to a solution of pyrrole and 4-dimethylaminopyridine (DMAP) (*cat.*) in dichloromethane under nitrogen atmosphere, and the mixture was stirred at room temperature. The solvent was removed under reduced pressure, giving the crude product which was purified with a thin layer of silica gel and eluting with dichloromethane / hexane (20:1) to obtain the desired product.

1-*tert*-Butyl 2-methyl 4-phenyl-1*H*-pyrrole-1,2-dicarboxylate (200)



The general procedure for *N*-Boc protection was followed using pyrrole **61** (41.5 mg, 0.206 mmol), Boc_2O (49.0 mg, 0.225 mmol) and DMAP (26.5 mg, 0.21 mmol) in dichloromethane (2 mL). The desired product **200** was obtained as a clear yellow oil in 65% yield.

MS: Found: M^+, 301.3359. $C_{17}H_{19}NO_4$ requires M^+, 301.3372.

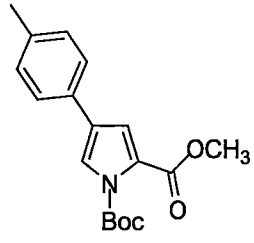
m/z (EI): 301 (20%, M^+), 201 (80), 169 (100), 153 (50), 141 (15), 84 (50).

IR ν_{max} (cm^{-1}): 3503, 2982, 2952, 1750, 1729, 1455, 1438, 1395, 1370, 1341, 1288, 1253, 1154, 1075, 845, 758.

^{1}H NMR δ: 1.60 (s, 9H), 3.87 (s, 3H), 7.13 (d, *J* = 2.1 Hz, 1H), 7.23 – 7.28 (m, 1H), 7.34 – 3.79 (m, 2H), 7.48 – 7.51 (m, 2H), 7.58 (d, *J* = 2.1 Hz, 1H).

^{13}C NMR δ: 28.5, 51.4, 80.9, 114.8, 120.0, 127.5, 127.1, 129.3, 129.5, 131.3, 133.4, 150.6, 159.9.

1-*tert*-Butyl 2-methyl 4-*p*-tolyl-1*H*-pyrrole-1,2-dicarboxylate (201)



The general procedure for *N*-Boc protection was followed using pyrrole **62** (22.7 mg, 0.105 mmol), Boc_2O (30.7 mg, 0.150 mmol) and DMAP (12.6 mg, 0.103 mmol) in dichloromethane (2mL). The title compound was obtained as a yellow oil in quantitative yield.

MS: Found: M^+, 315.0482. $C_{18}H_{21}NO_4$ requires M^+, 315.0470.

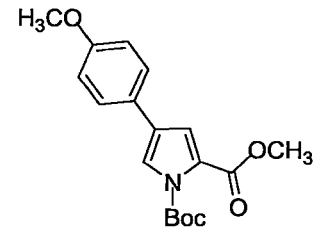
m/z (EI): 315 (10%, M^+), 215 (60), 183 (100), 140 (15), 128 (10), 115 (15), 57 (15).

IR ν_{max} (cm^{-1}): 3315, 2981, 2952, 2924, 1735, 1715, 1704, 1695, 1472, 1436, 1394, 1339, 1253, 1156, 1076, 820, 775.

^{1}H NMR δ: 1.60 (s, 9H), 2.35 (s, 3H), 3.87 (s, 3H), 7.12 (d, *J* = 2.0 Hz, 1H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 1.9 Hz, 1H).

^{13}C NMR δ: 27.79, 29.82, 52.11, 85.10, 118.94, 122.07, 125.49, 125.90, 126.05, 129.61, 130.26, 136.91, 151.61, 159.71.

1-*tert*-Butyl 2-methyl 4-(4-methoxyphenyl)-1*H*-pyrrole-1,2-dicarboxylate (202)



The general method for *N*-Boc protection was followed using pyrrole **60** (71.6 mg, 0.309 mmol), Boc_2O (77.5 mg, 0.355 mmol) and DMAP (20.3 mg, 0.166 mmol) in dry dichloromethane (3 mL). The title compound was obtained as yellow oil in quantitative yield.

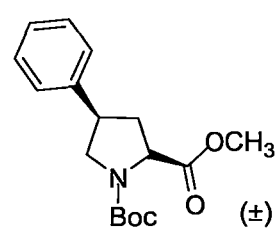
MS: Found: M^+, 331.1433. $C_{18}H_{21}NO_5$ requires M^+, 331.1402.

m/z (EI): 311 (10%, M^+), 211 (60), 179 (100), 136 (15), 123 (10), 60 (30).

^{1}H NMR δ: 1.60 (s, 9H), 3.82 (s, 3H), 3.87 (s, 3H), 6.86 – 6.93 (m, 2H), 7.08 (d, *J* = 1.8, 1H), 7.41 – 7.45 (m, 2H), 7.49 (d, *J* = 1.8 Hz, 1H).

^{13}C NMR δ: 27.39, 28.56, 28.92, 51.16, 56.38, 82.79, 113.44, 115.20, 122.34, 121.23, 126.05, 129.70, 149.46, 152.11.

(±) *cis*-1-*tert*-Butyl 2-methyl 4-phenylpyrrolidine-1,2-dicarboxylate (203)



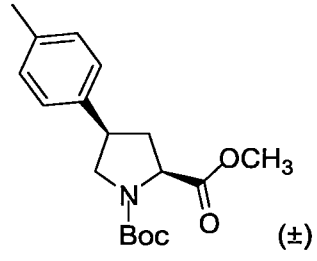
N-Boc pyrrole **200** (18.7 mg, 0.061 mmol) in methanol (5 mL) containing 10% w/w palladium on carbon (15 mg) was subjected to the standard catalytic hydrogenation procedure. After purification by passing the crude product through a plug of silica gel, eluting with 50% ethyl acetate / hexanes, the title compound was obtained in

68% yield as a clear oily solid. The spectral data reported as a mixture of carbamate rotomers and was consistent with that reported in literature.[120]

^{1}H NMR δ: 1.43 (s, 9H), 2.00 – 2.15 (m, 1H), 2.60 – 2.70 (m, 1H), 3.35 – 3.48 (m, 2H), 3.74 (s, 3H), 4.10 – 4.39 (m, 1H), 4.30 – 4.42 (m, 1H), 7.21 – 7.28 (m, 3H), 7.29 – 7.35 (m, 2H).

^{13}C NMR δ: 28.51, 28.63, 38.38, 43.20, 52.72, 59.82, 80.92, 127.26, 127.38, 128.92, 138.76, 152.56, 159.56.

(±) *cis*-1-*tert*-Butyl 2-methyl 4-*p*-tolylpyrrolidine-1,2-dicarboxylate (204)



(±)

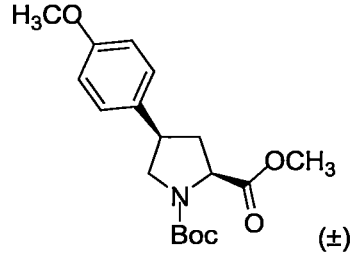
A mixture of *N*-Boc pyrrole **201** (21 mg, 0.089 mmol) and 5% w/w platinum on carbon (19.9 mg) in methanol (5 mL) was hydrogenated under 1 atmosphere of hydrogen (balloon) for 16 h at room temperature. The catalyst was removed by filtration through Celite. The crude product was obtained in 61% yield as a clear semi-solid and used without further purifications. The spectral data reported as a mixture of carbamate rotomers.

IR ν_{max} (cm^{-1}): 3363, 2925, 2853, 1690, 1360, 1258, 1201, 1158, 815.

^{1}H NMR δ: 1.56 (s, 9H), 1.61 – 1.71 (m, 1H), 2.16 – 1.96 (m, 1H), 2.31 (s, 3H), 2.61 – 2.67 (m, 1H), 3.23 – 3.53 (m, 2H), 3.70 – 3.76 (m, 3H), 4.35 – 4.42 (m, 1H), 7.13 (m, 4H).

^{13}C NMR δ: 28.50, 30.78, 35.05, 38.46, 43.71, 52.26, 59.38, 80.42, 127.25, 129.57, 137.01, 160.99, 171.02.

(±)-*cis*-1-*tert*-Butyl 2-methyl 4-(4-methoxyphenyl)pyrrolidine-1,2-dicarboxylate (205)

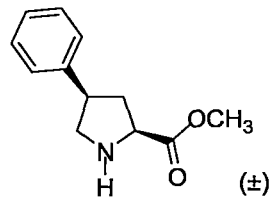


The standard catalytic hydrogenation conditions were followed using *N*-Boc pyrrole **202** (130.3 mg, 0.393 mmol) and palladium on carbon (20 mg) in methanol (5.0 mL). The crude product was purified by column chromatography (30% ethyl acetate / hexanes) to give the title compound **205** in 74% yield as a clear semi-solid. The spectral data reported as a mixture of carbamate rotomers.

^{1}H NMR δ: 1.41 (s, 9H), 1.85 – 2.15 (m, 1H), 2.57 - 2.65 (m, 1H), 3.28 – 3.46 (m, 2H), 3.77 (s, 3H), 3.98 - 4.02 (m, 1H), 4.27 – 4.41 (m, 1H), 6.90 – 6.80 (m, 2H), 7.14 (m, 2H).

GENERAL PROCEDURE FOR *N*-BOC DEPROTECTION

(±)-*cis*-Methyl 4-phenylpyrrolidine-2-carboxylate (206)



N-Boc pyrrolidine **203** (14.8 mg, 0.048 mmol) was dissolved in methanol (0.5 mL) and cooled to 0°C. A solution of HCl in methanol was prepared by the careful addition of thionyl chloride (0.1 mL) to methanol (0.3 mL), and the solution added slowly and stirred for 16 h at room temperature. The solvent was removed under reduced pressure yielding the product as the hydrochloric salt. The product was purified by passing through a thin layer of silica gel (50% ethyl acetate / hexanes, followed by 95% methanol / ammonia as eluents) to give the title compound in 98% yield as a colourless oil.

MS: Found: $[M-H]^+$, 204.1103. $C_{12}H_{14}NO_2$ requires $[M-H]^+$, 204.1103.

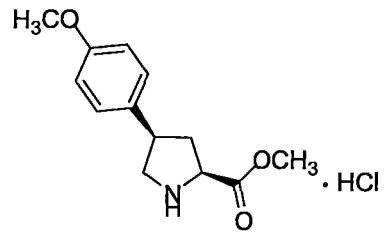
m/z (EI): 204 (80%, $[M-H]^+$), 188 (20), 169 (26), 146 (100), 129 (27), 104 (25), 71 (30), 57 (38).

IR ν_{max} (cm^{-1}): 3396, 2953, 2925, 2853, 1734, 1288, 1257, 1158, 1124, 1074, 1031, 699.

^1H NMR (D_2O) δ: 1.97 – 2.11 (m, 1H), 2.64 – 2.68 (m, 1H), 3.37 – 3.48 (m, 1H), 3.69 – 3.73 (m, 1H), 3.77 (s, 3H), 3.85 – 3.88 (m, 1H), 4.50 – 4.60 (m, 1H), 7.21 – 7.30 (m, 5H).

^{13}C NMR (D_2O): 37.05, 44.28, 51.03, 51.48, 61.94, 127.03, 127.44, 128.10, 128.80, 159.42.

(±)-*cis*-Methyl 4-(4-methoxyphenyl)pyrrolidine-2-carboxylate hydrochloride (207)



N-Boc pyrrolidine **205** (43.1 mg, mmol) was dissolved in methanol (0.5 mL). A solution mixture of HCl in methanol (methanol (0.3 mL) / thionylchloride (0.2 mL)) was added dropwise at 0°C. The mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure to give the title compound as hydrochloride salt in 64% yield.

MS: Found: $[M\text{-}H+D]^+$, 236.1262. $C_{13}H_{17}NO_3$ $[M\text{-}H+D^+]$, requires 236.1271.

m/z (EI): 236 (8%, $[M\text{-}H+D]^+$, $C_{13}H_{16}DNO_3$), 234 (10%, $[M\text{-}H]^+$, $C_{13}H_{16}NO_3$), 192 (15), 177 (98), 153 (25), 135 (100), 125 (32), 102 (20), 77 (21), 69 (28), 39 (75).

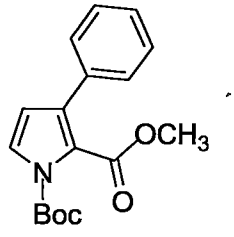
IR ν_{max} (cm^{-1}): 3390, 2960, 2929, 2870, 1765, 1709, 1514, 1464, 1439, 1394, 1369, 1291, 1248, 1177, 1148, 1071, 1032, 832.

^1H NMR (D_2O) δ: 2.24 (dt, *J* = 13.1, 10.9 Hz, 1H), 2.76 – 2.88 (m, 1H), 3.31 – 3.43 (t, *J* = 11.07 Hz, 1H), 3.55 – 3.66 (m, 1H), 3.81 (s, 3H), 3.83 (s, 3H), 3.86 – 3.97 (m, 1H), 4.64 (dd, *J* = 10.4, 7.6 Hz, 1H), 6.93 – 7.10 (m, 2H), 7.20 – 7.35 (m, 2H).

^{13}C NMR (D_2O) δ: 35.62, 42.28, 47.42, 51.21, 55.48, 60.21, 114.54, 128.52, 130.10, 158.27, 172.10.

6.3.2 Formation of 3-cis-Aryl-Proline Analogues

1-*tert*-Butyl 2-methyl 3-phenyl-1*H*-pyrrole-1,2-dicarboxylate (208)



The general procedure for the *N*-Boc protection was followed using pyrrole **75** (17.6 mg, 0.087 mmol), Boc_2O (33 mg, 0.151 mmol), and DMAP (10 mg, 0.012 mmol) in dichloromethane (2 mL) and the mixture was stirred for 3 h. The title compound was obtained as a clear yellow oil in 87% yield.

MS: Found: M^+, 301.3371. $C_{17}H_{19}NO_4$ requires M^+, 301.3372.

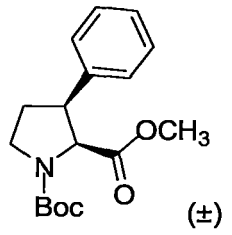
m/z (EI): 301 (10%, M^+), 201 (50), 169 (100), 153 (20), 141 (10), 84 (50).

IR ν_{max} (cm^{-1}): 2981, 2950, 1748, 1606, 1565, 1500, 1449, 1436, 1410, 1339, 1287, 1273, 1259, 1239, 1154, 1094, 747.

^1H NMR δ: 1.58 (s, 9H), 3.79 (s, 3H), 6.33 (d, *J* = 3.3 Hz, 1H), 7.26 – 7.40 (m, 5H), 7.44 – 7.47 (m, 1H)

^{13}C NMR δ: 27.82, 53.77, 98.78, 110.79, 120.54, 121.61, 128.73, 129.87, 138.22, 139.26, 148.23, 158.33, 160.23.

(±)-*cis*-1-tert-butyl 2-methyl 3-phenylpyrrolidine-1,2-dicarboxylate (209)

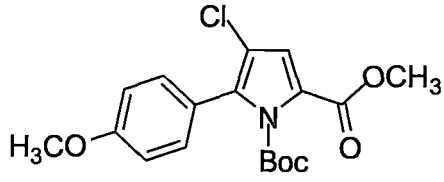


A mixture of *N*-Boc pyrrole **208** (16 mg, 0.053 mmol) and 10% w/w palladium on carbon (20.4 mg) in methanol (5 mL) was hydrogenated under 1 atmosphere of hydrogen (balloon) for 16 h at room temperature. The catalyst was removed by filtration through Celite. After filtration through a plug of silica gel eluting with 50% ethyl acetate / hexane, the title product was obtained in 68% yield as clear semi-solid and used without further purifications. The spectral data was reported as a 3:2 mixture of carbamate rotomers and was consistent with that reported in literature.[100]

^{1}H NMR δ: 1.32 – 1.53 (m, 9H), 2.13 (s, 1H), 2.55 (s, 1H), 3.16 – 3.32 (m, 3H), 3.37 – 3.52 (m, 1H), 3.70 (d, *J* = 2.9 Hz, 1H), 4.46 (d, *J* = 8.7 Hz, 0.6H), 4.55 (d, *J* = 8.8 Hz, 0.4H), 7.00 – 7.50 (m, 5H).

^{13}C NMR δ: 28.56, 45.98, 46.22, 47.56, 48.22, 51.28, 51.56, 64.03, 64.51, 80.45, 80.55, 127.32, 127.65, 127.96, 128.34, 128.56, 128.59, 136.78, 136.89, 153.28, 170.89.

1-*tert*-Butyl 2-methyl 4-chloro-5-(4-methoxyphenyl)-1*H*-pyrrole-1,2-dicarboxylate (212)



The title compound was prepared following the general procedure for *N*-Boc protection. Pyrrole **67** (18.4 mg, 0.069 mmol), Boc_2O (25.4 mg, 0.084 mmol) and DMAP (5.4 mg, 0.044 mmol) in dichloromethane (1.5 mL) were stirred for 4 h. The solvent was removed under pressure to give the crude product. The title compound **212** was obtained in a quantitative yield as a semi-solid.

MS: Found: M^+, 365.1064. $C_{18}H_{20}ClNO_5$ requires M^+, 365.1039.

m/z (EI): 367 (2%,M^+, $C_{20}H_{18}{}^{37}ClNO_4$), 365 (5%, M^+, $C_{20}H_{18}{}^{35}ClNO_4$), 302 (64), 265 (95), 233 (50), 210 (55), 128 (100), 99 (32), 57 (75).

^{1}H NMR δ: 1.37 (s, 9H), 3.85 (s, 6H), 6.88 (s, 1H), 6.95 (m, 2H), 7.35 (m, 2H).

^{13}C NMR δ: 27.28, 52.04, 55.43, 85.96, 112.84, 113.75, 117.37, 121.04, 122.05, 131.52, 134.57, 148.78, 160.18, 160.23.

6.4 Experimental Procedures for Compounds Described in Chapter 4

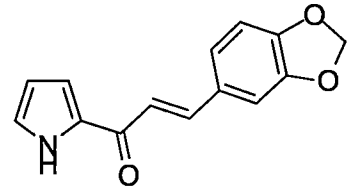
6.4.1 Formation of α,β-unsaturated ketopyrroles

GENERAL PROCEDURE FOR ALDOL CONDENSATION

To a mixture of 2-acetyl pyrrole, 2M sodium hydroxide and potassium hydroxide, the corresponding aldehyde was added at 0°C. The reaction was stirred at room temperature for 16 h. During this time, a precipitate formed and the product

filtered. The product can be purified further *via* recrystallisation from ethanol if required.

(*E*)-3-(Benzo[d][1,3]dioxol-5-yl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one (220)



The general procedure of aldol condensation was followed using 2-acetylpyrrole (5.0632 g, 46.4 mmol), piperonal (6.972 g, 46.4 mmol) and potassium hydroxide (250 mg, 4.4 mmol)) in 2M sodium hydroxide (10mL) and ethanol (50 mL). The crude product was purified by recrystallisation from ethanol to give **220** as a yellow solid in 91% yield. Crystals suitable for X-ray crystallography were grown from ethanol.

Melting point: 155 – 158 °C

MS: Found: M^+, 241.0737. $C_{14}H_{11}NO_3$ requires M^+, 241.0739.

m/z (EI): 241 (100%, M^+), 224 (10), 212 (20), 183 (10), 154 (20), 117 (10), 94 (15).

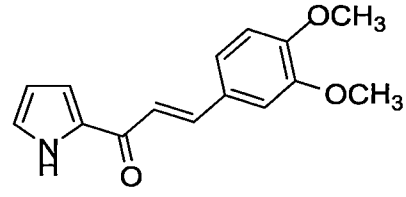
IR ν_{max} (cm^{-1}): 3246, 1642, 1635, 1621, 1506, 1487, 1445, 1256, 1239, 1100, 1038.

^{1}H NMR δ: 6.02 (s, 2H) 6.35 (dt, *J* = 3.9, 2.5 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 7.04 – 7.07 (m, 1H), 7.09 – 7.15 (m, 2H), 7.15 – 7.18 (m, 1.5H), 7.22 (s, 0.5H), 7.75 (d, *J* = 15.6 Hz, 1H), 9.91 (bs, H).

^{13}C NMR δ: 101.69, 106.75, 108.75, 111.04, 116.18, 120.12, 125.01, 125.33, 129.58, 133.32, 142.20, 148.44, 178.97.

Crystal data: $C_{14}H_{11}NO_3$, *M* = 241.24, triclinic, space group *P*-1, *a* = 10.300(3), *b* = 10.846(2), *c* = 10.916(14)Å, α =86.91(4), β = 72.78(4), γ = 84.45(2)°, *V* = 1159.1(16)Å^3, *Z* = 4, *Dc* = 1.382 g cm^{-3}, specimen: yellow block, 0.46 x 0.44 x 0.44 mm, 4291 measured reflections, *R*int = 0.015, *R* = 0.044 for 3038 'observed' data ((*I*) >2σ(*I*)), *wR* = 0.1126, and GOOF = 1.017 for all data '4056'.

(*E*)-3-(3,4-Dimethoxyphenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one (221)



The title compound was obtained following the standard aldol condensation using 2-acetylpyrrole (5.0313 g, 46.2 mmol), veratraldehyde (8.2730 g, 49.8 mmol), 2M sodium hydroxide (10 mL) and potassium hydroxide (250 mg, 4.4 mmol) in ethanol (30 mL). The crude product was filtered and recrystallised from ethanol to give the desired product in 85% as a yellow crystalline solid.

Melting point: 160 – 164 °C

MS: Found: M^+, 257.1054. $C_{14}H_{11}NO_3$ requires M^+, 257.1052.

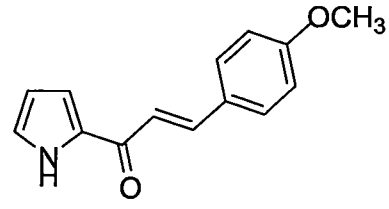
m/z (EI): 257 (M^+, 45%), 226 (50), 195 (100), 120 (45), 94 (20), 78 (30).

IR ν_{max} (cm^{-1}): 3262, 1640, 1584, 1512, 1422, 1405, 1271, 1138, 1109, 1054.

^{1}H NMR δ: 3.93 (s, 3H), 3.96 (s, 3H), 6.33 – 6.37 (m, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 7.06 – 7.13 (m, 2H), 7.15 (d, *J* = 2.0 Hz, 1H), 7.19 – 7.26 (m, 2H), 7.78 (d, *J* = 15.6 Hz, 1H), 9.88 (bs, 1H).

^{13}C NMR δ: 56.08, 56.11, 110.16, 111.00, 111.19, 116.14, 119.92, 122.97, 125.26, 128.08, 133.34, 142.53, 149.27, 151.25, 161.25.

(*E*)-3-(4-Methoxyphenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one (222)



The general procedure of aldol condensation was followed using 2-acetylpyrrole (5.0388 g, 46.2 mmol), anisaldehyde (6.4902 g, 47.7 mmol), 2M sodium hydroxide (10mL) and potassium hydroxide (250 mg, 4.4 mmol) in ethanol (30 mL). The precipitate was collected and recrystallised from ethanol to give the title compound **222** as a light yellow crystalline solid suitable for X-ray analysis in 90% yield.

IR ν_{max} (cm^{-1}): 3255, 1642, 1605, 1569, 1543, 1510, 1423, 1404, 1250, 1173, 1110, 1055.

^{1}H NMR δ: 3.86 (s, 3H), 6.35 (dt, *J* = 3.8, 2.5 Hz, 1H), 6.89 – 6.98 (m, 2H), 7.04 – 7.12 (m, 2H), 7.27 (d, *J* = 15.0 Hz, 1H), 7.55 – 7.65 (m, 2H), 7.80 (d, *J* = 15.6 Hz, 1H), 9.81 (bs, 1H)

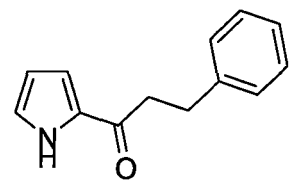
^{13}C NMR δ: 55.54, 111.01, 114.47, 116.01, 119.73, 125.13, 130.17, 133.39, 142.20, 155.80, 156.72, 161.52.

Crystal data: $C_{14}H_{13}NO_2$, *M* = 227.25, monoclinic, space group $P2_1/c$, *a* = 5.099(8), *b* = 16.979(5), *c* = 13.929(6)Å, α =90, β = 99.07(4), γ = 90°, *V* = 1191(2))Å^3, *Z* = 4, *D*c = 1.267 g cm^{-3}, specimen: yellow block, 0.44 x 0.44 x 0.42 mm, 2180 measured reflections, *R*int = 0.035, *R* = 0.053

for 1614 'observed' data ((I) >2σ(I)), wR = 0.155, and GOOF = 1.102 for all data '2093'.

6.4.2 Formation of α,β-saturated ketopyrroles

3-Phenyl-1-(1*H*-pyrrol-2-yl)propan-1-one (223)

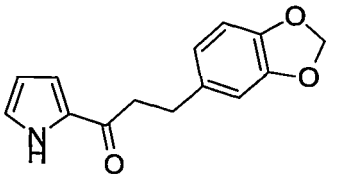


(*E*)-3-Phenyl-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one (207.0 mg, 1.05 mmol) was subjected to catalytic hydrogenation with 10% w/w palladium on carbon (20.6mg) in ethanol (10mL) under an atmosphere of hydrogen using a balloon for 16 h. The catalyst was removed by filtrating through Celite and concentrated under reduced pressure. The compound was obtained as a light yellow solid in 95% yield and used without further purification.

^{1}H NMR δ: 2.99 – 3.20 (m, 4H), 6.28 (dt, J = 3.9, 2.5 Hz, 1H), 6.92 - 6.93 (m, 1H), 7.03 – 7.04 (m, 1H), 7.13 – 7.39 (m, 5H), 9.94 (s, 1H).

^{13}C NMR δ: 30.89, 39.70, 110.69, 116.50, 125.01, 126.21, 128.47, 128.59, 131.86, 141.35, 189.92.

3-(Benzo[d][1,3]dioxol-5-yl)-1-(1*H*-pyrrol-2-yl)propan-1-one (224)



The general procedure for catalytic hydrogenation was carried with pyrrole **220** (7.3200 g, 32.2 mmol) and 10% w/w palladium on carbon (0.100 g) in ethanol (150mL). After recrystallisation from ethanol, the product was obtained as crystalline yellow solids suitable for X-ray analysis in 86% yield.

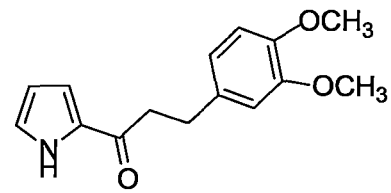
IR ν_{max} (cm^{-1}): 3282, 1635, 1545, 1502, 1490, 1443, 1429, 1404, 1246, 1109, 1097, 1039, 931, 749.

^{1}H NMR δ: 2.91 - 3.13 (m, 4H), 5.92 (s, 2H), 6.27 (dt, *J* = 3.9, 2.5 Hz, 1H), 6.59 – 6.78 (m, 3H), 6.88 – 6.91 (m, 1H), 7.02 – 7.04 (m, 1H), 9.67 (bs, 1H).

^{13}C NMR δ: 30.63, 39.98, 100.93, 108.36, 109.00, 110.76, 116.36, 121.24, 124.82, 135.14, 145.91, 147.70, 189.75.

Crystal data: $C_{14}H_{13}NO_3$, *M* = 243.25, monoclinic, space group $P2_1/n$, *a* = 12.846(3), *b* = 4.852(5), *c* = 18.919(3)Å, α =90, β = 91.42(2), γ = 90°, *V* = 1178.9(12)Å^3, *Z* = 4, *D*c = 1.371 g cm^{-3}, specimen: yellow block, 0.42 x 0.42 x 0.42 mm, 2126 measured reflections, *R*int = 0.073, *R* = 0.054 for 1634 'observed' data ((*I*) >2σ(*I*)), *wR* = 0.156, and GOOF = 1.028 for all data '2061'.

3-(3,4-Dimethoxyphenyl)-1-(1*H*-pyrrol-2-yl)propan-1-one (225)



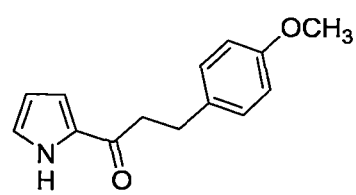
The title compound was formed by the general procedure for catalytic hydrogenation using pyrrole **221** (1.0095g, 3.92 mmol) and 10% w/w palladium on carbon (50.5 mg) in methanol (100mL). After recrystallisation from ethanol, the product **225** was obtained as a yellow solid in 86% yield.

IR ν_{max} (cm^{-1}): 3285, 1633, 1627, 1515, 1403, 1399, 1261, 1234, 1139, 1108, 1028.

^{1}H NMR δ: 2.87 - 3.20 (m, 4H), 3.85 (s, 6H), 6.27 (dt, *J* = 3.9, 2.5 Hz, 1H), 6.76 – 6.81 (m, 3H), 6.86 – 6.93 (m, 1H), 7.00 – 7.07 (m, 1H), 9.59 (bs, 1H).

^{13}C NMR δ: 30.61, 39.97, 55.93, 56.03, 110.84, 111.35, 111.82, 116.43, 120.22, 124.85, 131.94, 133.92, 147.46, 148.95, 189.85.

3-(4-Methoxyphenyl)-1-(1*H*-pyrrol-2-yl)propan-1-one (226)



Pyrrole **222** (3.9708 g, 18.6 mmol) with 10% w/w palladium on carbon (204.7 mg) in ethanol (100 mL) was stirred at room temperature for 16 h under an atmosphere of hydrogen (balloon). The desired compound **226** was obtained as a yellow solid in 80% yield after recrystallisation from ethanol.

IR ν_{max} (cm^{-1}): 3278, 1633, 1512, 1403, 1246.

^{1}H NMR δ: 2.98 – 3.15 (m, 4H), 6.26 (dt, *J* = 3.6, 2.4 Hz, 1H), 6.84 (td, *J* = 2.1, 8.7 Hz, 2H), 6.85 – 6.93 (m, 1H), 7.032 (dt, *J* = 1.5, 2.4 Hz, 1H), 7.16 (td, *J* = 2.1, 8.4 Hz, 2H), 9.76 (bs, 1H).

^{13}C NMR δ: 30.07, 40.03, 55.38, 110.72, 113.99, 116.35, 124.80, 129.41, 131.93, 133.39, 158.04, 189.99.

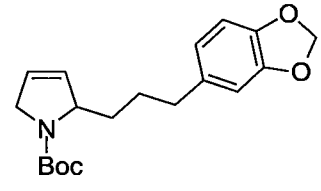
6.4.3 Partial Reduction using Zinc / HCl

N-Boc pyrrolines were obtained using the following two-step reaction.

GENERAL PROCEDURE: PARTIAL REDUCTION *VIA* ZINC/HCL FOLLOWED BY *N*-BOC PROTECTION

To a hot solution of pyrrole in methanol, powdered zinc (10 equiv.) and concentrated hydrochloric acid were added in small portions, such that the solution was refluxing. The reaction was cooled and made alkaline with concentrated ammonia and extracted with dichloromethane. The combined organic extracts were dried and removed under reduced pressure. The mixture was then subjected to the general procedure for the *N*-Boc protection as previously described to give the desired product after purification by column chromatography.

tert-Butyl 2-(3-(benzo[d][1,3]dioxol-5-yl)propyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (243)



The general procedure for the Zn/HCl reduction was followed using pyrrole **224** (0.5268 g, 2.16 mmol), powdered zinc (1.4717g, 22.5 mmol), concentrated

hydrochloric acid (15 mL) and methanol (12 mL). After purification *via* column chromatography (50% ethyl acetate / hexanes as eluent), the 4:1 mixture of **229** and **230** was obtained in quantitative yield as a dark brown oil, which was then subjected to the general procedure for *N*-Boc protection using Boc_2O (664.4 mg, 2.207 mmol), DMAP (16.8 mg, 0.137 mmol) and dichloromethane (10 mL), stirring at room temperature for 16 h. The mixture of products was purified by column chromatography (20% ethyl acetate / hexanes as eluent) to yield **243** isolated pure in 79% yield over-2-steps from pyrrole **224**, as light yellow oil. The saturated pyrrolidine **244** was also isolated in 10% yield as a light yellow oil. The following spectral data was reported as a mixture of carbamate rotomers.

Spectral Data for **243** (Major):

The spectral data reported as a mixture of carbamate rotomers.

MS: Found: M^+, 331.1786. $C_{19}H_{25}NO_4$ requires M^+, 331.1784.

m/z (EI): 331 (20%, M^+), 274 (30), 258 (10), 230 (30), 213 (10), 148 (100), 135 (80), 112 (70), 83 (40), 68 (75), 57 (65), 41 (30).

IR ν_{max} (cm^{-1}): 2978, 2911, 1697, 1503, 1490, 1442, 1395, 1368, 1245, 1212, 1171, 1120, 1071, 1039.

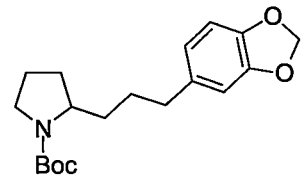
^1H NMR δ: 1.48 (s, 9H), 1.70 – 1.73 (m, 2H), 2.49 – 2.51 (m, 2H), 3.09 – 3.33 (m, 2H) 3.95 – 4.20 (m, 2H), 4.40 – 4.52 (m, 1H), 5.65 – 5.76 (m, 2H), 5.91 (s, 2H), 6.57 – 6.72 (m, 3H).

^{13}C NMR δ: 27.64, 28.11, 28.62, 26.25, 33.43, 35.95, 53.97, 64.11, 85.41, 100.92, 108.27, 109.04, 121.27, 125.43, 130.19, 148.76.

Spectral Data for **244** (Minor):

The spectral data reported as a mixture of carbamate rotomers.

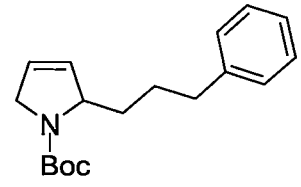
***tert*-Butyl 2-(3-(benzo[d][1,3]dioxol-5-yl)propyl)pyrrolidine-1-carboxylate (244)**



^{1}H NMR δ: 1.42 (s, 9H), 1.46 – 1.57 (m, 2H), 1.70 – 1.75 (m, 2H), 2.25 – 2.43 (m, 2H), 2.52 (t, *J* = 7.5 Hz, 1H), 2.66 – 2.76 (m, 2H), 2.87 (t, *J* = 7.8 Hz, 1H), 3.09 (dd, *J* = 7.8, 6.3 Hz, 1H), 3.21 (t, *J* = 7.5 Hz, 1H), 4.07 – 4.14 (m, 1H), 5.88 – 5.91 (m, 2H), 6.58 – 6.72 (m, 3H).

^{13}C NMR δ: 25.52, 28.49, 29.85, 34.88, 35.42, 40.18, 41.92, 60.45, 82.45, 100.87, 108.22, 108.24, 108.94, 109.05, 121.29, 129.94, 152.57.

***tert*-Butyl 2-(3-phenylpropyl)-2,5-dihydro-1H-pyrrole-1-carboxylate (241)**



The general procedure for Zn/HCl was followed using pyrrole **223** (158.3 mg, 0.795 mmol), powdered zinc (416.0 mg, 11.75 mmol) and concentrated hydrochloric acid (6 mL) in methanol (6 mL) over a period of 5 min. A 5:1 mixture of **227** and **228** was obtained in quantitative yield as a dark brown oil, and reacted under the general procedure for *N*-Boc protection using Boc_2O (157.5 mg, 0.52 mmol), DMAP (15.2 mg, 0.12 mmol) and dichloromethane (10 mL), stirring at

room temperature for 16 h. The crude mixture was purified by column chromatography (10% ethyl acetate / hexanes as eluent) and obtained **241** pure in 35% yield over-2-steps from **223** as a yellow oil. Compound **242** was isolated in 2% yield as a clear oil.

Spectral Data for **241** (Major):

The spectral data was reported as a 1:1 mixture of carbamate rotomers.

MS: Found: M^+, 287.1976. $C_{18}H_{25}NO_2$ requires M^+, 287.1991.

m/z (EI): 287 (1%, M^+), 231 (10), 168 (30), 112 (100), 91 (20), 80 (7), 68 (75), 57 (70), 41 (15).

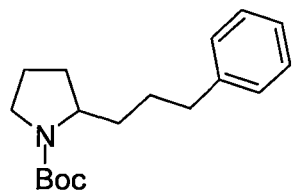
^{1}H NMR δ: 1.41 (s, 9H), 1.52 – 1.57 (m, 2H), 1.65 – 1.80 (m, 2H), 2.58 – 2.63 (m, 2H), 3.94 – 4.04 (m, 1H), 4.11 – 4.24 (m, 1H), 4.40 – 4.53 (m, 0.5H), 4.53 – 4.61 (m, 0.5H), 5.65 – 5.78 (m, 2H), 7.14 – 7.29 (m, 5H).

^{13}C NMR δ: 25.99, 26.70, 27.49, 27.70, 28.55, 28.64, 33.26, 33.58, 36.07, 36.16, 53.73, 53.95, 63.87, 64.12, 79.24, 79.37, 125.18, 125.37, 125.74, 125.83, 128.38, 128.43, 130.00, 130.145, 142.36, 142.76, 153.90, 154.40.

Spectral Data for **242** (Minor):

The spectral was data reported as a mixture of carbamate rotomers.

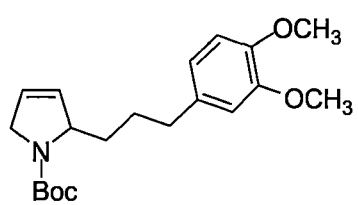
***tert*-Butyl 2-(3-phenylpropyl)pyrrolidine-1-carboxylate (242)**



^{1}H NMR δ: 0.85 – 0.87 (m, 2H), 1.59 (s, 9H), 1.65 – 1.75 (m, 2H), 1.85 – 1.95 (m, 4H), 2.39 – 2.47 (m, 2H), 2.58 – 2.63 (m, 2H), 3.09 – 3.11 (m, 1H), 7.05 – 7.12 (m, 5H).

^{13}C NMR δ: 27.66, 28.54, 28.61, 33.65, 35.21, 40.03, 42.13, 61.62, 125.98, 126.04, 128.53, 130.06, 142.67, 151.76.

***tert*-Butyl 2-(3-(3,4-dimethoxyphenyl)propyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (245)**



The general procedure of Zn/HCl reduction was followed, using pyrrole **225** (501.2 mg, 1.94 mmol) in methanol (30 mL), powdered zinc (1.3254 g, 20.2 mmol) and concentrated hydrochloric acid (10 mL) over a period of 5 min. A 5: 1 mixture of **231** and **232** was obtained in quantitative yield as a dark brown oil, and reacted with Boc_2O (703.4 mg, 2.33 mmol) and DMAP (21.9 mg, 0.179 mmol) in dichloromethane (10 mL) under the general procedure for *N*-Boc protection. The mixture was purified by column chromatography (30% ethyl acetate / hexanes as

eluent). **245** was isolated in 64% yield over-2-steps from **225** as a light yellow oil. The saturated pyrrolidine **246** was isolated in 3% yield as a clear oil.

Spectral Data for **245** (Major):

The spectral data was reported as a 1:1 mixture of carbamate rotomers.

MS: Found: M^+, 345.2089. $C_{20}H_{29}NO_4$ requires M^+, 345.2097.

m/z (EI): 345 (10%, M^+), 289 (15), 246 (80), 164 (75), 151 (50), 137 (10), 112 (50), 81 (70), 68 (80), 57 (100), 41 (25).

IR ν_{max} (cm^{-1}): 2974, 2934, 2861, 1694, 1684, 1590, 1455, 1367, 1156, 1139, 1030.

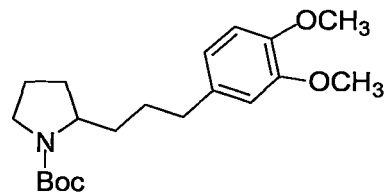
^1H NMR δ: 1.29 – 1.46 (m, 9H), 1.63 – 1.73 (m, 2H), 1.82 (dt, *J* = 25.9, 9.4 Hz, 1H), 2.36 (dd, *J* = 7.2, 2.5 Hz, 1H), 2.51 (t, *J* = 7.5 Hz, 2H), 2.95 – 3.09 (m, 1H) 3.81 (s, 3H), 3.83 (s, 3H), 3.99 – 4.21 (m, 1H), 4.37 – 4.60 (m, 1H), 5.66 (m, 2H), 6.80 – 6.57 (m, 3H).

^{13}C NMR δ: 23.97, 25.33, 26.09, 26.841, 27.57, 28.45, 33.12, 33.50, 35.55, 39.79, 39.95, 41.86, 53.60, 53.78, 55.70, 55.90, 63.74, 63.95, 79.18, 111.11, 111.61, 111.66, 120.11, 120.21, 125.03, 125.17, 129.89, 134.13, 134.91, 135.26, 147.05, 147.16, 148.67, 148.76, 154.21, 156.01, 156.81.

Spectral Data for **246** (Minor):

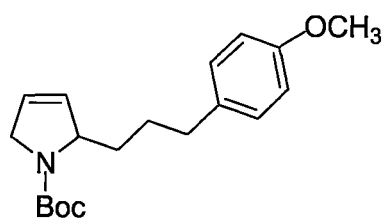
The spectral data was reported as a mixture of carbamate rotomers.

tert-butyl 2-(3-(3,4-dimethoxyphenyl)propyl)pyrrolidine-1-carboxylate (246)



^{1}H NMR δ: 1.41 (s, 9H), 1.46 – 1.56 (m, 2H), 1.69 – 1.79 (m, 2H), 1.84 – 1.91 (m, 2H), 2.40 (td, *J* = 2.7, 11.7 Hz, 2H), 2.54 (t, *J* = 6.9 Hz, 2H), 2.89 – 2.92 (m, 1H), 3.06 – 3.15 (m, 1H), 3.23 – 3.35 (m, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 6.67 – 6.78 (m, 3H).

***tert*-Butyl 2-(3-(4-methoxyphenyl)propyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (247)**



The general procedure of Zn/HCl reduction was performed. Powdered zinc (414.2 mg, 6.33 mmol) and concentrated hydrochloric acid (6 mL) were added to a mixture of pyrrole **226** (135.9 mg, 0.59 mmol) in methanol (30 mL) over a period of 5 min. A 5:1 mixture of **233** and **234** was obtained in quantitative yield as a dark brown oil, and reacted with Boc_2O (157.5 mg, 0.52 mmol) and DMAP (15.2 mg, 0.12 mmol) in dichloromethane (10 mL) under the general procedure for *N*-Boc protection. The crude mixture was purified by column chromatography (10% ethyl acetate / hexanes as eluent) and **247** was isolated in 45% yield over-2-steps from

226 as a light yellow oil. The saturated pyrrolidine **248** was isolated in 14% yield as a clear oil.

Spectral Data for **247** (Major):

The spectral data was reported as a mixture of carbamate rotomers.

IR ν_{max} (cm^{-1}): 2976, 2934, 1715, 1654, 1512, 1368, 1246, 1176, 1163.

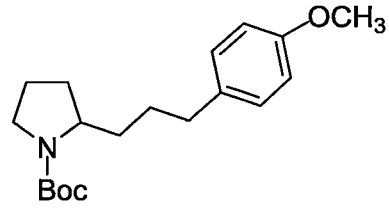
^{1}H NMR δ: 1.45 (m, 9H), 1.58 (m, 2H), 1.65 – 1.76 (m, 2H), 2.48 – 2.60 (m, 2H), 3.77 (s, 3H), 3.94 – 4.02 (m, 1H), 4.12 – 4.15 (m, 1H), 4.45 – 4.52 (m, 1H), 5.66 – 5.76 (m, 2H), 6.78 – 6.83 (m, 2H), 7.04 – 7.08 (m, 2H).

^{13}C NMR δ: 28.60, 33.40, 35.18, 53.83, 55.32, 60.48, 64.01, 79.30, 113.77, 125.25, 129.32, 130.10, 134.65, 154.34, 157.76.

Spectral Data for **248** (Minor):

The spectral data was reported as a mixture of carbamate rotomers.

***tert*-Butyl 2-(3-(4-methoxyphenyl)propyl)pyrrolidine-1-carboxylate (248)**



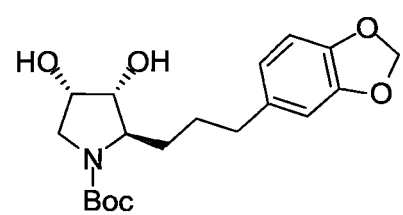
^{1}H NMR δ: 1.46 (s, 9H), 1.65 – 1.74 (m, 2H), 1.82 – 1.92 (m, 4H), 2.38 – 2.43 (m, 2H), 2.51 – 2.65 (m, 3H), 2.85 – 2.89 (m, 1), 3.04 – 3.13 (m, 1H), 3.77 (s, 3H), 7.05 – 7.12 (m, 4H).

6.4.4 Dihydroxylations of Pyrroline Intermediates

GENERAL PROCEDURE FOR DIHYDROXYLATION

A catalytic amount of osmium tetraoxide (2 wt% in H_2O) and 4-morphilone-*N*-oxide (NMO) (50 wt% in H_2O) were added to a solution of pyrroline in acetone and water (9:1) under a nitrogen atmosphere, and the reaction stirred at room temperature for 16 h. The mixture was quenched by the addition of saturated sodium sulfite and brine, followed by the extraction with ethyl acetate. The combined organic extracts were concentrated to give the crude product.

(±)-(2*R*,3*R*,4*S*)-*tert*-Butyl 2-(3-(benzo[d][1,3]dioxol-5-yl)propyl)-3,4-dihydroxypyrrolidine-1-carboxylate (249)



The general procedure of dihydroxylation was followed, using *N*-Boc pyrroline **243** (122.3 mg, 0.37 mmol), osmium tetraoxide (30 µL of 2 wt% in H_2O, 0.02 mmol), and NMO (175 µL of 50 wt% in H_2O, 0.84 mmol) in acetone / water (9:1, 1 mL). The product was purified *via* column chromatography (97:3 dichloromethane / methanol as eluent) to give the title compound in 89% yield as a yellow oil. The spectral data was reported as a mixture of carbamate rotomers.

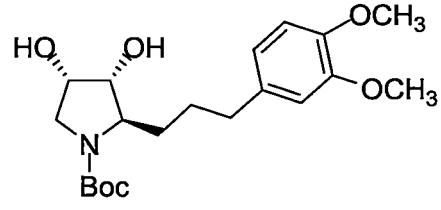
MS: Found: M^+, 365.1836. $C_{19}H_{27}NO_6$ requires M^+, 365.1838.

m/z (EI): 365 (20%, M^+), 309 (95), 264 (30), 248 (10), 205 (10), 175 (20), 148 (100), 135 (55), 102 (50), 57 (80).

^{1}H NMR δ: 1.22 – 1.27 (m, 2H), 1.41 (s, 9H), 1.56 – 1.61 (m, 2H), 2.50 – 2.62 (m, 2H), 2.71 (s, 2H), 3.29 – 3.41 (m, 1H), 3.50 (dd, *J* = 11.4, 6.3 Hz, 1H), 3.61 – 3.72 (m, 1H), 3.86 – 3.91 (m, 1H), 4.23 (dd, *J* = 10.5, 6.1 Hz, 1H), 5.90 (s, 2H), 6.76 – 6.54 (m, 3H).

^{13}C NMR δ: 27.98, 28.53, 32.01, 35.64, 36.05, 50.57, 63.32, 69.93, 79.92, 100.84, 108.21, 108.92, 121.20, 145.67, 155.04.

(±)-(2*R*,3*R*,4*S*)-*tert*-Butyl 2-(3-(3,4-dimethoxyphenyl)propyl)-3,4-dihydroxypyrrolidine-1-carboxylate (250)



Dihydroxylation was carried out by the general procedure, using pyrroline **245** (99.8 mg, 0.28 mmol), OsO_4 (30 µL of 2 wt% in H_2O, 0.02 mmol) and NMO (133µL of 50 wt% in H_2O, 0.63 mmol) in acetone / water (9:1, 1 mL). After column chromatography (20% ethyl acetate / hexanes, followed by 97:3 dichloromethane / methanol as eluent), the desired product **250** was obtained in 62% yield as yellow oil. The ring-opened product **255** was obtained in 12% yield as a clear oil.

Spectral data for **250**:

The spectral data was reported as a mixture of carbamate rotomers.

MS: Found: M^+, 380.2149. $C_{20}H_{31}NO_6$ requires M^+, 381.2151.

m/z (EI): 381 (25%, M^+), 325 (70), 280 (30), 191 (20), 164 (80), 151 (75), 102 (25), 57 (100), 41 (20).

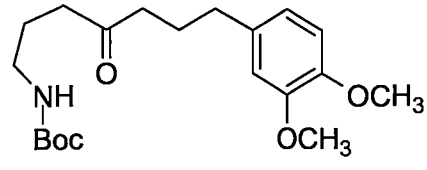
IR ν_{max} (cm^{-1}): 3391, 2972, 2934, 1690, 1684, 1669, 1516, 1435, 1416, 1366, 1260, 1236, 1155, 1139, 1089, 1029.

^1H NMR δ: 1.37 (m, 9H), 1.54 – 1.64 (m, 2H), 2.42 – 2.56 (m, 2H), 3.20 – 3.55 (m, 3H), 3.56 – 3.62 (m, 1H), 3.66 – 3.69 (m, 1H), 3.81 (s, 3H), 3.83 (s, 3H), 3.86 – 3.89 (m, 1H), 4.20 (dd, *J* = 10.5, 6.1 Hz, 1H), 6.62 – 6.76 (m, 3H).

^{13}C NMR δ: 27.70, 28.42, 32.17, 35.44, 50.26, 55.83, 55.95, 63.22, 69.53, 75.77, 79.91, 111.25, 111.75, 120.21, 134.72, 147.12, 148.76, 155.06.

Spectral Data for **255**:

***tert*-Butyl 7-(3,4-dimethoxyphenyl)-4-oxoheptylcarbamate (255)**



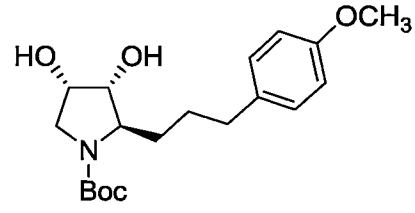
m/z (EI): 365 (60, M^+), 338 (10), 310 (40), 292 (10), 266 (100), 249 (40), 207 (15).

IR ν_{max} (cm^{-1}): 3380, 2932, 1709, 1516, 1464, 1453, 1365, 1260, 1168, 1157, 1209.

^{1}H NMR δ: 1.42 (s, 9H), 1.74 (dt, *J* = 12.0, 6.0 Hz, 2H), 1.88 (dt, *J* = 14.9, 7.4 Hz, 2H), 2.41 (td, *J* = 7.2, 3.0 Hz, 4H), 2.49 – 2.61 (at, 2H), 3.10 (dd, *J* = 12.9, 6.6 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.57 (bs, 1H), 6.72 – 6.65 (m, 2H), 6.78 (d, *J* = 8.6 Hz, 1H).

^{13}C NMR δ: 24.16, 25.52, 28.52, 34.82, 40.03, 40.14, 42.11, 55.94, 56.03, 71.15, 111.26, 111.77, 120.38, 134.31, 147.36, 148.95, 158.46, 170.65.

(±)-(2*R*,3*R*,4*S*)-*tert*-Butyl 3,4-dihydroxy-2-(3-(4-methoxyphenyl)propyl)pyrrolidine-1-carboxylate (251)



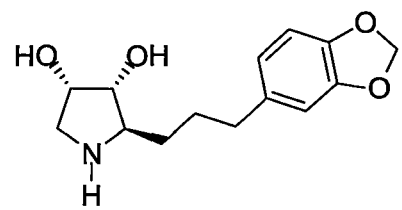
The general procedure for dihydroxylation was followed, using *N*-Boc pyrroline **247** (21.5 mg, 0.069 mmol), OsO_4 (30 µL of 2 wt% in H_2O, 0.02 mmol) and NMO (31 µL of 50 wt% in H_2O, 0.135 mmol) in acetone/water (9:1, 1 mL). The crude product was purified *via* column chromatography (97:3 dichloromethane/methanol as eluent) to give the title product in 86% as a yellow oil. The spectral data was reported as a mixture of carbamate rotomers.

^{1}H NMR δ: 1.41 (s, 9H), 1.55 – 1.65 (m, 2H), 2.52 – 2.60 (m, 2H), 2.78 (bs, 2H), 3.35 – 3.40 (m, 1H), 3.50 (dd, *J* = 11.6, 6.5 Hz, 1H), 3.63 – 3.69 (m, 1H), 3.77 (s, 3H), 3.89 – 3.92 (m, 1H), 4.21 – 4.25 (m, 1H), 6.82 (m, 2H), 7.08 (m, 2H).

^{13}C NMR δ: 28.07, 28.64, 32.19, 35.12, 50.66, 55.49, 63.49, 70.10, 75.64, 80.01, 113.97, 129.47, 132.56, 138.32, 155.15, 157.95.

6.4.5 N-Boc Deprotection

(±)-(2*R*,3*R*,4*S*)-2-(3-(Benzo[d][1,3]dioxol-5-yl)propyl)pyrrolidine-3,4-diol (257)

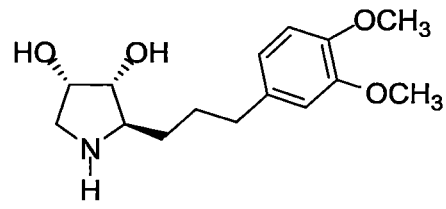


N-Boc pyrrolidine **249** (60.7 mg, 0.17 mmol) was dissolved in methanol (1.0 mL). A solution of HCl in methanol (methanol / thionyl chloride (5:1), 0.5 mL) was added slowly at 0°C, and the mixture stirred at room temperature for 0.5 h. The solvent was removed and the crude mixture was passed through a thin layer of silica gel eluting with 50% ethyl acetate / hexanes, followed by methanol / ammonia (4:1). The amino-diol **257** was obtained as 67% yield.

^{1}H NMR (D_2O) δ: 1.65 – 1.83 (m, 4H), 2.55 – 2.60 (m, 2H), 3.24 – 3.31 (m, 1H), 3.43 – 3.49 (m, 2H), 3.96 – 4.00 (dd, *J* = 8.5, 4.0 Hz, 1H), 4.30 – 4.35 (m, 1H), 5.89 (s, 2H), 6.76 (m, 3H).

^{13}C NMR (D_2O) δ: 27.76, 29.24, 34.27, 49.07, 60.63, 69.41, 75.05, 100.91, 108.51, 109.14, 121.56, 136.03, 145.24, 147.19.

(±)-(2*R*,3*R*,4*S*)-2-(3-(3,4-Dimethoxyphenyl)propyl)pyrrolidine-3,4-diol (256)



N-Boc deprotection was followed as described for **250**, using *N*-Boc pyrrolidine **225** (29.1 mg, 0.076 mmol) and a solution of HCl in methanol (methanol / thionyl chloride (5:1), 0.5 mL). The desired product was obtained after column chromatography (100% ethyl acetate, followed by 95:5 methanol/ammonia as eluent), in 78% yield as a clear oil.

HRMS: Found: M^+, 281.1622. $C_{15}H_{23}NO_4$ requires M^+, 281.1627.

m/z: 281 (20%, M^+), 191 (35), 164 (100), 151 (30), 115 (15), 102 (50), 91 (10), 70 (25), 56 (15), 44 (25).

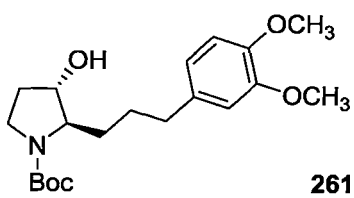
^{1}H NMR (D_2O) δ: 1.67 – 1.84 (m, 4H), 2.56 – 2.65 (m, 3H), 3.16 – 3.28 (m, 1H), 3.43 – 3.52 (m, 2H), 3.73 (s, 3H) ,3.75 (s, 3H), 3.92 (dd, *J* = 8.5, 4.2 Hz, 1H), 4.24 - 4.29 (m, 1H), 6.76 – 6.88 (m, 3H).

^{13}C NMR (D_2O) δ: 27.61, 29.21, 34.03, 49.01, 55.70, 55.83, 60.60, 69.36, 74.99, 112.06, 112.42, 114.30, 118.17, 121.00, 135.34.

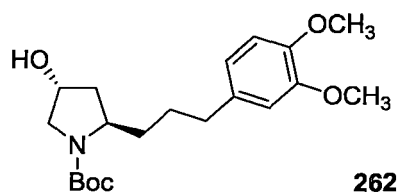
6.4.6 Monohydroxylation of Pyrroline Intermediates

(±)-(2*R*,3*S*)-*tert*-Butyl 2-(3-(3,4-dimethoxyphenyl)propyl)-3-hydroxypyrrolidine-1-carboxylate (261) and

(±)-(2*R*,4*R*)-*tert*-Butyl 2-(3-(3,4-dimethoxyphenyl)propyl)-3-hydroxypyrrolidine-1-carboxylate (262)



261



262

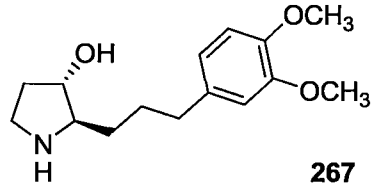
To a mixture of *N*-Boc pyrroline **245** (35.4 mg, 0.102 mmol) in THF (2 mL), borane-methyl sulphide (75.6 µL, 0.15 mmol) was added slowly at 0°C. The reaction was warmed to room temperature and stirred for 3 h. A mixture of 6M sodium hydroxide (3 mL) and 30% hydrogen peroxide (1 mL) was added slowly at 0°C, and the mixture stirred for a further 16 h at room temperature. Saturated potassium carbonate and brine were added and extracted with ethyl acetate. The combined organic extracts were dried with sodium sulphate and concentrated under reduced pressure. A 1:1 mixture of **261** and **262** was isolated after a column chromatography with increasing eluent strength (30%, 50% and 100% ethyl acetate / hexanes as eluent) in 82% combined yield. The spectral data was reported as a mixture of carbamate rotomers.

^{1}H NMR δ: 1.17 - 1.33 (m, 4H), 1.42 (s, 18H), 1.45 – 2.08 (m, 12H), 2.43 – 2.66 (m, 4H), 3.12 (dd, *J* = 12.7, 6.7 Hz, 1H), 3.29 – 3.43(m, 1H), 3.43 – 3.55 (m, 1H), 3.60 – 3.70 (m, 1H), 3.84 (s, 6H), 3.86 (s, 6H), 4.05 – 4.13 (m, 1H), 4.28 – 4.41 (m, 1H), 6.61 – 6.84 (m, 6H).

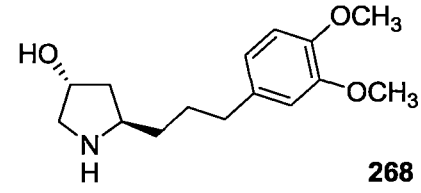
^{13}C NMR δ: 26.70, 27.96, 28.74, 28.79, 30.01, 31.99, 33.14, 34.63, 34.77, 35.18, 35.74, 35.84, 37.50, 40.40, 44.15, 55.01, 56.13, 56.26, 56.45, 57.24, 66.56, 70.15, 71.75, 74.69, 79.63, 79.71, 111.56, 112.07, 120.45, 135.32, 147.46, 149.12, 155.25, 155.33.

(*R*)-2-(3-(3,4-dimethoxyphenyl)propyl)pyrrolidin-3-ol 267 and

(*R*)-5-(3-(3,4-dimethoxyphenyl)propyl)pyrrolidin-3-ol 268



267



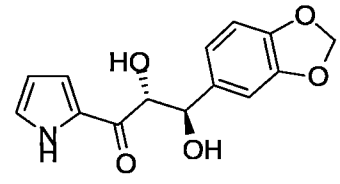
268

N-Boc deprotection was followed as described for **257** using the mixture of **261** and **262** (15 mg, 0.056 mmol) and a solution of HCl in methanol (methanol / thionyl chloride (3:2), 1.0 mL). The crude mixture was purified *via* column chromatography (95% methanol / ammonia as eluent) to give a 1:1 mixture of **267** and **268** isolated in 70% combined yield.

^{1}H NMR (CD_3OD) δ: 1.33 – 1.51 (m, 2H), 1.89 – 2.06 (m, 2H), 2.08 – 2.32 (m, 3H), 2.54 – 2.70 (m, 3H), 2.70 – 2.78 (m, 1H), 2.87 – 2.97 (m, 1H), 3.10 – 3.23 (m, 2H), 3.42 – 3.48 (m, 7H), 3.55 – 3.65 (m, 1H), 3.79 (s, 6H), 3.92 (s, 6H), 4.09 – 4.28 (m, 1H), 4.45 – 4.56 (m, 1H), 6.67 – 6.94 (m, 6H).

^{13}C NMR (CD_3OD) δ: 29.02, 29.22, 32.63, 32.83, 33.00, 34.08, 34.39, 35.17, 35.262, 36.78, 41.44, 43.65, 54.13, 55.19, 55.36, 55.46, 57.48, 66.28, 71.46, 76.37, 111.89, 112.28, 113.67, 120.49, 130.25, 135.48, 147.40, 149.13.

(2*R*,3*R*)-3-(Benzo[d][1,3]dioxol-5-yl)-2,3-dihydroxy-1-(1*H*-pyrrol-2-yl)propan-1-one (272)

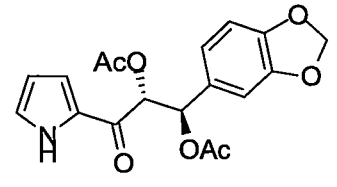


The general procedure for the dihydroxylation was followed using pyrrole **220** (264.2 mg, 1.09 mmoL), NMO (250 µL of 50 wt% in H_2O, 2.41 mmoL) and OsO_4 (30 µL of 2 wt% in H_2O, 0.02 mmol) in a mixture of acetone / water (9:1, 10 mL). The reaction mixture was stirred for 16 h at room temperature. The desired product **272** was isolated after a column chromatography (50% ethyl acetate / hexanes as eluent) in 38% yield.

^{1}H NMR δ: 4.82 (d, *J* = 3.6, 1H), 4.90 (d, *J* = 3.3, 1H), 5.92 – 5.93 (m, 2H), 6.25 – 6.37 (m, 3H), 6.80 – 6.83 (m, 3H), 7.06 – 7.09 (m, 2H), 9.82 (s, 1H).

^{13}C NMR δ: 76.24, 77.26, 101.29, 107.29, 108.33, 111.66, 112.67, 118.54, 120.11, 124.49, 126.59, 147.55, 148.01, 178.12.

(±)-(1*R*,2*R*)-1-(Benzo[d][1,3]dioxol-5-yl)-2,3-diacetoxy-3-(1*H*-pyrrol-2-yl)propane-1-one (273)



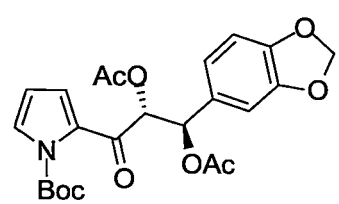
To a stirring mixture of pyrrole **272** (93.4 mg, 0.339 mmol) in dichloromethane (5 mL), dry pyridine (75 µL, 0.088 mmol) and acetyl chloride (63.2 mg, 0.80 mmol)

were added at 0°C. The reaction mixture was stirred at room temperature for 6 h. The reaction was washed with saturated potassium hydrogen sulphate (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with 2M sodium carbonate (2 x 10 mL) and dried with sodium sulphate. The solvent was evaporated under reduced pressure, and purified by column chromatography (50% ethyl acetate / hexanes as eluent) to yield the title compound in 87% yield.

^{1}H NMR δ: 2.03 (s, 3H), 2.12 (s, 3H), 5.83 (d, *J* = 6.0 Hz, 1H), 5.91 (s, 2H), 6.21 (d, *J* = 6.3 Hz, 1H) 6.24 – 6.26 (m, 1H), 6.69 (d, *J* = 8.1 Hz, 1H), 6.79 – 6.86 (m, 2H), 6.99 – 7.04 (m, 2H), 9.97 (bs, 1H).

^{13}C NMR δ: 20.74, 20.95, 74.37, 76.68, 101.24, 107.72, 108.23, 111.27, 118.39, 121.18, 126.64, 129.44, 129.76, 147.74, 147.68, 169.64, 169.90, 182.65.

(±)-(1*R*,2*R*)-1-(Benzo[d][1,3]dioxol-5-yl)-2,3-diacetoxy-3-(1-(*tert*-butoxycarbonyl)-1*H*-pyrrol-2-yl)-propane-1-one (274)



To obtain the title compound, pyrrole **273** (26.8 mg, 0.074 mmol) was subjected to the standard *N*-Boc protection procedure with Boc_2O (23.7 mg, 0.108 mmol) and

DMAP (5.3 mg, 0.043 mmol) in dry dichloromethane (1 mL). The title compound was obtained in quantitative yield as a clear oil.

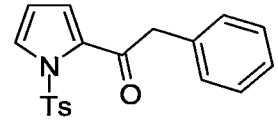
^{1}H NMR δ: 1.55 (s, 9H), 2.05 (s, 3H), 2.08 (s, 3H), 5.84 (d, *J* = 5.1 Hz, 1H), 5.88 – 5.91 (m, 2H), 6.14 – 6.16 (at, 1H), 6.19 (d, *J* = 5.1 Hz, 1H), 6.60 – 6.73 (m, 1H), 6.83 – 6.90 (m, 2H), 6.97 – 6.98 (dd, *J* = 1.8, 3.9 Hz, 1H), 7.33 – 7.34 (dd, *J* = 1.5, 3.0 Hz, 1H),

^{13}C NMR δ: 20.71, 21.01, 27.65, 73.97, 77.71, 85.18, 101.25, 107.66, 108.24, 110.44, 120.98, 122.78, 129.27, 129.84, 130.95, 147.77, 147.81, 148.15, 169.53, 169.83, 183.56.

6.5 Experimental Procedures for Compounds Described in Chapter 5

6.5.1 Formation of N-sulfonyl pyrrolines

2-Phenyl-1-(1-*tosyl*-1*H*-pyrrol-2-yl)ethanone (288)



Phenyl-acetic acid (1.3022 g, 9.56 mmol) was slowly added to a mixture of *N*-tosyl pyrrole **275** (1.0373 g, 4.69 mmol) in TFAA (5.0 mL) and dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 16 h. The volatiles were removed under reduced pressure; water (20 mL) and saturated sodium carbonate (10 mL) were added, and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were dried and filtered through a thin layer of silica gel eluting with dichloromethane. The solvent was removed using rotary evaporation

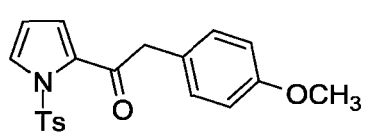
and the crude product purified *via* column chromatography (50% ethyl acetate / hexanes as eluent). The desired product was obtained in 52% yield. The spectral data was consistent with that reported in literature.[159]

IR ν_{max} (cm^{-1}): 3248, 3145, 3015, 1675, 1594, 1498, 1435, 1421, 1366, 1190, 1172, 1142, 1090, 1065, 1020.

^{1}H NMR δ: 2.41 (s, 3H), 3.96 (s, 2H), 6.29 – 6.32 (m, 1H), 7.07 (dd, *J* = 3.8, 1.7 Hz, 1H), 7.11 – 7.14 (m, 2H), 7.02 - 7.29 (m, 5H), 7.79 (dd, *J* = 3.2, 1.7 Hz, 1H), 7.87 (d, 2H),

^{13}C NMR δ: 21.84, 46.59, 110.48, 124.31, 126.97, 128.48 (x2), 128.74, 129.24, 129.44 (x2), 130.58, 134.73, 144.88, 198.44.

2-(4-Methoxyphenyl)-1-(1-*tosyl*-1*H*-pyrrol-2-yl)ethanone (289)



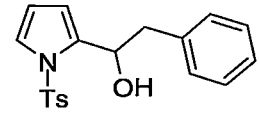
The title compound was prepared using the above procedure for **288**, using *N*-tosyl pyrrole **275** (1.1221 g, 5.08 mmol), TFAA (5.0 mL) and *p*-methoxyphenylacetic acid (1.3022 g, 9.56 mmol) in dichloromethane (15 mL). The reaction mixture was stirred at room temperature for 16 h. The desired product was obtained in 62% as a yellow oil after column chromatography (20% ethyl acetate-hexanes as eluent). The spectral data was consistent with that reported in literature.[159]

^{1}H NMR δ: 2.40 (s, 3H), 3.76 (s, 3H), 3.91 (s, 2H), 6.32 (at, *J* = 1.5, 1H), 6.75 – 6.80 (m, 3H), 7.03 – 7.09 (m, 3H), 7.26 – 7.28 (m, 2H), 7.79 (dd, *J* = 3.2, 1.7 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 2H).

^{13}C NMR δ: 21.76, 45.64, 55.29, 110.49, 114.14, 114.83, 116.11, 124.26, 128.39, 129.41, 130.50, 132.93, 135.80, 144.85, 158.55, 186.46.

6.5.2 Partial Reduction of N-Sulfonyl Pyrroles

2-Phenyl-1-(1-*tosyl*-1*H*-pyrrol-2-yl)ethanol (291)



Sodium borohydride (74 mg, 1.96 mmol) was added to a solution of ketone **288** (168.4 mg, 0.50 mmol) in 1:3 mixture of dichloromethane and ethanol (15 mL), and the reaction stirred at room temperature for 16 h. The volatiles were removed under reduced pressure, water (20 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic extracts were dried and concentrated to yield the title compound as dark yellow oil in 45% yield.

MS: Found: $[M - H_2O]^+$, 323.1056. $C_{19}H_{18}NO_2S$ requires $[M - H_2O]^+$, 323.1086.

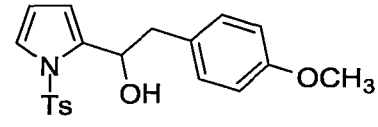
m/z (EI): 340 (1%, $[M-1]^+$), 323 (30), 264 (100), 250 (45), 168 (70), 155 (52), 91 (87), 61 (10).

IR ν_{max} (cm^{-1}): 3556, 3254, 3150, 2942, 1596, 1496, 1453, 1362, 1189, 1174, 1149, 1127, 1090, 1077, 1056, 813, 726, 673, 592.

^{1}H NMR δ: 2.40 (s, 3H), 2.71 (bs, 1H), 3.01 (dd, *J* = 13.8, 8.5 Hz, 1H), 3.16 (dd, *J* = 13.8, 4.9 Hz, 1H), 5.17 (dd, *J* = 8.5, 4.9 Hz, 1H), 6.26 (t, *J* = 3.3 Hz, 1H), 6.33 – 6.35 (m, 1H), 7.12 – 7.29 (m, 8H), 7.64 (d, *J* = 8.3 Hz, 2H).

^{13}C NMR δ: 21.64, 42.38, 66.81, 111.73, 112.779, 123.41, 126.45, 126.61, 128.38, 129.34, 130.06, 136.24, 129.42, 138.21, 145.10.

2-(4-Methoxyphenyl)-1-(1-*tosyl*-1*H*-pyrrol-2-yl)ethanol (292)



The title compound was prepared following the procedure for **291** using ketone **289** (261.2 mg, 0.81 mmol) and sodium borohydride (100.6 mg, 2.66 mmol) in a mixture of 1:3 dichloromethane and ethanol (15 mL). The title compound was obtained as a dark-yellow oil in 84% yield after purification *via* column chromatography (20% ethyl acetate-hexanes as eluent).

MS: Found: M^+, 368.1165. $C_{20}H_{19}NO_4S$ requires M^+, 368.1191.

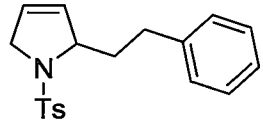
m/z (EI): 368 (20%, M^+), 248 (100), 155 (85), 121 (78), 91 (80).

^{1}H NMR δ: 2.40 (s, 3H), 2.96 (dd, *J* = 13.9, 8.5 Hz, 1H), 3.11 (dd, *J* = 13.9, 4.8 Hz, 1H), 3.78 (d, *J* = 2.4 Hz, 3H), 5.11 (dt, *J* = 8.7, 4.4 Hz, 1H), 6.25 (t, *J* = 3.4 Hz, 1H), 6.29 – 6.38 (m, 1H), 6.71 – 6.38 (m, 2H), 7.02 – 7.10 (m, 2H), 7.21 – 7.27 (m, 2H), 7.29 (dd, *J* = 3.3, 1.7 Hz, 1H), 7.59 – 7.67 (m, 2H).

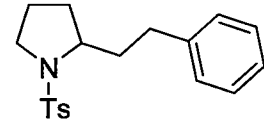
^{13}C NMR δ: 21.81, 41.57, 55.33, 67.06, 111.79, 112.81, 113.91, 123.51, 126.70, 130.12, 130.24, 130.39, 136.37, 137.51, 145.17, 158.34.

2-Phenethyl-1-*tosyl*-2,5-dihydro-1*H*-pyrrole (293) and

2-Phenethyl-1-*tosyl*pyrrolidine (294)



293



294

To a solution of *N*-tosyl pyrrole **291** (177.3 mg, 0.519 mmol) in dichloromethane / TFA (4:2, 5 mL), sodium cyanoborohydride (112.0 mg, 1.78 mmol) was carefully added at 0°C. The mixture was stirred at room temperature for 16 h. The volatiles were removed under reduced pressure, 2M sodium carbonate (15 mL) was added, and extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried and concentrated by rotary evaporation to give the crude product. Purification *via* column chromatography (20% ethyl acetate/hexanes as eluent) gave an inseparable 3:1 mixture of **293** and **294** in quantitative yield. Spectral data for both compounds is consistent with that reported in literature.[160,161]

Spectral Data for **293** (Major):

^{1}H NMR δ: 2.01 – 2.18 (m, 2H), 2.38 (s, 3H), 2.51 – 2.84 (m, 2H), 4.02 – 4.13 (m, 1H), 4.42 – 4.60 (m, 2H), 5.52 – 5.69 (m, 2H), 7.21 – 7.33 (m, 7H), 7.64 – 7.71 (m, 2H).

^{13}C NMR δ: 21.78, 31.02, 37.66, 56.06, 67.00, 125.15, 126.06, 127.65, 128.61, 128.70, 129.82, 129.94, 130.01, 141.93, 143.66.

Spectral Data for **294** (Minor)[#]:

MS: Found: M^+, 329.1438. $C_{18}H_{21}NO_5$ requires M^+, 329.1449.

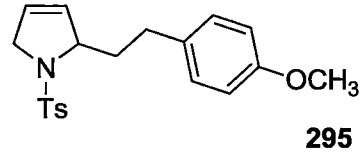
m/z (EI): 329 (3%, M^+), 224 (100), 155 (45), 91 (55), 70 (20).

^{1}H NMR δ: 1.41 – 1.53 (m, 3H), 1.72 – 1.83 (m, 2H), 2.18 – 2.26 (m, 1H), 2.41 (s, 3H), 2.58 – 2.75 (m, 2H), 3.20 – 3.25 (m, 1H), 3.37 – 3.45 (m, 1H), 3.51 – 3.61 (m, 1H), 7.21 – 7.33 (m, 5H), 7.33 – 7.63 (m, 2H), 7.58 – 7.65 (m, 2H).

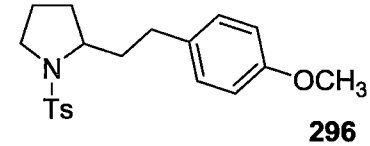
^{13}C NMR δ: 21.64, 24.21, 30.88, 32.50, 37.82, 49.20, 59.94, 125.96, 126.53, 126.98, 127.68, 128.59, 129.14, 129.69, 129.72.

2-(4-Methoxyphenethyl)-1-*tosyl*-2,5-dihydro-1*H*-pyrrole (295) &

2-(4-Methoxyphenethyl)-1-*tosyl*-pyrrolidine (296)



295



296

To a solution of *N*-tosyl pyrrole **292** (83.2 mg, 0.25 mmol) in 3:2 dichloromethane / TFA (1 mL), sodium cynoborohydride (47.7 mg, 0.76 mmol) was carefully added at 0°C. The mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure, 2M sodium carbonate (5 mL) was added and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried and concentrated by rotary evaporation to give the crude product. Purification *via* column chromatography (20% ethyl acetate / hexanes as eluent)

[#]Data obtained after isolation from the next synthetic sequence.

gave an inseparable 4:1 mixture of **295** and **296** in quantitative yield.

Spectral Data for **295** (Major):

^{1}H NMR δ: 1.98 – 2.15 (m, 2H), 2.38 (s, 3H), 2.48 – 2.61 (m, 2H), 3.76 (s, 3H), 4.02 – 4.21 (m, 2H), 4.40 – 4.54 (m, 1H), 5.52 – 5.67 (m, 2H), 6.81 – 6.86 (m, 2H), 7.09 – 7.12 (m, 2H), 7.25 – 7.28 (m, 2H), 7.64 – 7.66 (m, 2H).

^{13}C NMR δ: 21.59, 29.93, 37.73, 55.32, 55.85, 66.82, 113.80, 125.01, 127.47, 127.57, 129.39, 129.54, 129.75, 130.05, 133.78, 143.46.

Spectral Data for **296** (Minor)[#]:

MS: Found: $[M^{+1}]$ 360.1625. $C_{20}H_{25}NO_3S$ $[M^{+1}]$ requires 360.1628.

m/z (EI): 360 (100%, M^{+1}), 338 (10), 279 (20), 269 (15), 226 (50).

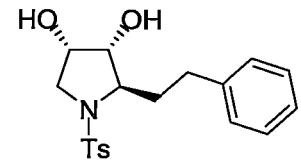
IR ν_{max} (cm^{-1}): 2952, 2875, 1215, 1342, 1246, 1176, 1159, 1091, 1036, 817, 663, 558.

^{1}H NMR δ: 1.36 – 1.54 (m, 1H), 1.54 – 1.64 (m, 2H), 1.65 – 1.86 (m, 1H), 2.08 – 2.27 (m, 1H), 2.47 (s, 3H), 2.50 – 2.72 (m, 2H), 3.13 – 3.27 (m, 1H), 3.35 – 3.46 (m, 1H), 3.51 – 3.63 (m, 1H), 3.80 (s, 3H), 3.99 – 4.23 (m, 1H), 6.79 – 6.90 (m, 2H), 7.08 – 7.16 (m, 2H), 7.20 – 7.29 (m, 2H), 7.58 – 7.65 (m, 2H).

^{13}C NMR δ: 21.66, 24.24, 30.91, 31.58, 38.07, 49.19, 55.43, 59.94, 113.90, 127.13, 127.67, 129.47, 129.69, 133.67, 133.79, 134.60.

6.5.3 Dihydroxylation of Pyrroline Intermediates

(±)-(2*R*,3*R*,4*S*)-2-Phenethyl-1-*tosyl*pyrrolidine-3,4-diol (304)



The general procedure for dihydroxylation was followed using the inseparable mixture of **293** and **294** (145 mg), OsO_4 (30 µL of 2 wt% in H_2O, 0.02 mmol) and NMO (249.7 µL of of 50 wt% in H_2O, 2.13 mmol) in acetone / water (9:1, 5mL) and stirred at room temperature for 16 h. After column chromatography of the crude product (20% ethyl acetate / hexanes, followed by 5% methanol / dichloromethane as eluent), the title compound was obtained in 43% yield over-2-steps from **291** as a yellow oil. The saturated compound **294** was isolated at 17% yield.

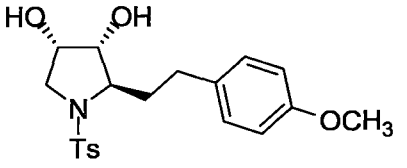
MS: Found: M^+ 361.1342. $C_{19}H_{23}NO_4S$ requires M^+, 361.1348.

m/z (EI): 361 (10%, M^+), 318 (14), 256 (40), 220 (12), 206 (20), 184 (30), 155 (62), 91 (100) 71 (22), 57 (30), 42 (15).

^{1}H NMR δ: 1.77 – 2.00 (m, 1H), 2.39 (s, 3H), 2.52 – 2.86 (m, 2H), 3.13 (dd, *J* = 10.5, 6.3 Hz, 1H), 3.36 – 3.53 (m, 1H), 3.58 (dd, *J* = 10.4, 5.9 Hz, 1H), 3.87 – 3.95 (m, 1H), 4.06 – 4.15 (m, 1H), 4.15 – 4.27 (m, 1H), 6.90 – 7.20 (m, 5H), 7.57 – 7.75 (m, 4H).

^{13}C NMR δ: 21.67, 31.06, 31.83, 35.48, 65.13, 70.09, 75.47, 126.08, 127.62, 127.97, 128.53, 128.61, 129.56, 129.82, 129.89.

1-((2*S*,3*R*,4*S*)-3,4-Dihydroxy-1-*tosyl*-pyrrolidin-2-yl)-2-(4-methoxyphenyl)ethanone (306)



The general procedure for dihydroxylation was followed using the mixture of **295** and **296**, OsO_4 (30 µL of 2 wt% in H_2O, 0.02 mmol) and NMO (79 µL, 9.25 mmol) in acetone / water (9:1, 1 mL) and stirred at room temperature for 16 h. Column chromatography of the crude product (30% ethyl acetate / hexanes, followed by 5% methanol / dichloromethane as eluent) gave the title compound in 46% yield over-2-steps from **292** as a yellow oil. The saturated pyrrolidine **296** was isolated in 14% yield.

MS: Found: M^+ 391.1453. $C_{20}H_{25}NO_5S$ requires 391.1453.

m/z (EI): 391 (10%, M^+), 236 (12), 224 (5), 155 (15), 134 (10), 121 (58), 102 (100), 91 (25).

^{1}H NMR δ: 1.71 – 1.91 (m, 1H), 2.05 – 2.23 (m, 1H), 2.30 (s, 3H), 2.46 – 2.62 (m, 1H), 2.62 – 2.77 (m, 1H), 3.12 (dd, *J* = 10.4, 6.4 Hz, 1H), 3.38 – 3.49 (m, 1H), 3.57 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.79 (s, 3H), 3.85 – 3.98 (m, 1H0, 4.14 – 4.26 (m, 1H), 6.73 – 6.89 (ad, 2H), 7.07 – 7.15 (ad, 2H), 7.21 – 7.28 (m, 1H), 7.57 – 7.65 (m, 1H).

^{13}C NMR δ: 21.69, 30.92, 35.70, 52.09, 55.39, 65.15, 70.13, 75.46, 113.62, 127.47, 127.96, 129.51, 129.60, 133.29, 143.74, 157.95.

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Appendices

Crystal structure data

Crystal structure data has been converted to *cif* file format, and providing in the following CD.